UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

Office of Chemical Safety and Pollution Prevention

MEMORANDUM

May 30, 2012

SUBJECT: **Difenoconazole** Human Health Risk Assessment for Postharvest Use on Tuberous and Corm Vegetables Subgroup 1C and Expansions of Existing Crop Group or Representative Commodity Uses to Fruiting Vegetables Group 8-10, Citrus Fruits Group 10-10, Pome Fruits Group 11-10, and Low growing Berry Subgroup 13-07G, Except Cranberry

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Decision No.: 447590

Petition No.: 1E7852
Risk Assessment Type: Single Chemical Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: D398616
Registration No.: 100-1262, 100-1312, 100-1313, 100-1317, and 100-1386
Regulatory Action: Section 3
Case No.: 7014
CAS No.: 119446-68-3
40 CFR: §180.475

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This document provides the Health Effects Division's (HED's) risk assessment of requested expanded use of difenoconazole on fruits, berries and a new postharvest use on tuberous and corm vegetables, subgroup 1C. Registration Division (RD) has informed HED that the petitioner is requesting a post harvest use on all commodities listed under Vegetables, tuberous and corm, subgroup 1C and not just potato as specified in Section B of the petition.

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY

This assessment provides information to support amended Section 3 registrations for the new postharvest use of difenoconazole on Tuberous and Corm Vegetables Subgroup 1C and the expansion of currently registered foliar uses for fruiting vegetables, citrus fruits, pome fruits, and strawberries to include the additional commodities specified under Fruiting Vegetables Group 8-10, Citrus Fruits Group 10-10, Pome Fruits Group 11-10, and Low growing Berry Subgroup 13-07G, Except Cranberry. This document assesses dietary and drinking water risks associated with exposures resulting from currently registered and proposed new uses of and tolerances for difenoconazole. It also assesses potential enhanced sensitivity of infants and children from dietary and/or residential exposure as required under the Food Quality Protection Act (FQPA) of 1996.

Use Profile

Difenoconazole is a broad spectrum fungicide belonging to the triazole group of fungicides. It is currently registered in the U.S. for use as a seed treatment on barley, canola, cotton, sweet corn, wheat, and triticale and for foliar application to numerous food crops and ornamentals. Tolerances for difenoconazole, currently established under 40 CFR §180.475, range from 0.01-95 ppm. Difenoconazole acts by blocking demethylation during sterol biosysnthesis which, in turn, disrupts membrane synthesis. Difenoconazole is available as emulsifiable concentrate, soluble concentrate, emulsion [oil] in water, flowable suspension, and ready-to-use formulations. As a seed treatment, it is applied with commercial grade seed treatment equipment. As a foliar treatment, it is applied to field and vegetable crops, landscape ornamentals and golf course turf by commercial applicators using aerial and ground application methods and equipment. It is applied to ornamentals by residential applicators using hand held sprayers.

<u>Proposed New Uses</u>

The Interregional Research Project No. 4 (IR-4) is requesting the following actions.

1) Establishment of tolerances for residues of difenoconazole in/on Fruiting Vegetables Group 8-10, Citrus Fruits Group 10-10, Pome Fruits Group 11-10, and Low growing Berry Subgroup 13-07G, Except Cranberry.
2) An increase in the existing tolerance in/on Vegetable, tuberous and corm, subgroup 1C from 0.01 ppm to 4.0 ppm;
3) Removal of existing tolerances in/on potato, processed waste, fruiting vegetable (group 8), citrus (group 10), pome fruit(group 11), and strawberry;
4) An amendment for the Section 3 registration for Thesis™ Fungicide (EPA Reg. No. 100-1386) to add a postharvest use on Vegetables, tuberous and corm, subgroup 1C (1 application at 0.0070 lb ai/ton tubers); and
5) Amendments for the Section 3 registrations for Inspire™ Fungicide (EPA Reg. No. 100-1262), Inspire™ XT Fungicide (EPA Reg. No. 100-1312), Quadris Top™ Fungicide (EPA Reg. No. 100-1313) and Inspire Super™ Fungicide (EPA Reg. No. 100-1317) to expand currently registered foliar uses for fruiting vegetables, citrus fruits, pome fruits,

and strawberries to include the additional commodities specified under the following new crop groups/subgroup; Fruiting Vegetables Group 8-10, Citrus Fruits Group 10-10, Pome Fruits Group 11-10, and Low growing Berry Subgroup 13-07G, Except Cranberry. No substantive changes to the currently registered foliar use patterns on the subject crops have been proposed.

Hazard Identification

Subchronic and chronic toxicity studies with difenoconazole in mice and rats showed decreased body weights, decreased body weight gains and effects on the liver. Acute and subchronic neurotoxicity studies showed evidence of neurotoxic effects. However, the observed effects were transient and the dose-response was well characterized with identified dose levels at which no observed adverse effects were seen. The available toxicity studies indicated no increased susceptibility of rats or rabbits from in utero or postnatal exposure to difenoconazole. There are no indications of immunotoxicity in the available studies. No evidence of carcinogenicity was seen in the chronic/cancer rat study. Evidence for carcinogenicity was seen in mice as induction of liver tumors at doses which were considered to be excessively high for carcinogenicity testing. Difenoconazole has been classified as "Suggestive Evidence of Carcinogenic Potential" with risk quantified using a non-linear (Margin of Exposure) approach. The cancer classification is based on excessive toxicity observed at the two highest doses, the absence of tumors at the lower doses and the absence of genotoxic effects. The FQPA Safety Factor is reduced to 1X. Difenoconazole exhibits low acute toxicity by the oral, dermal and inhalation routes of exposure. It is not an eye or skin irritant and is not a sensitizer.

The toxicological database for difenoconazole is sufficient to conduct this risk assessment. An immunotoxicity study, required under Part 158 Toxicology Data requirements, has been submitted and is under review.

Dose Response Assessment

Toxicological points of departure (PODs) were selected for dietary and drinking water exposures for the assessment of proposed new uses of difenoconazole. Acute and chronic PODs were selected for assessment of food and water exposures. An acute POD for all populations was selected from an acute neurotoxicity study in rats based on reduced grip strength. A chronic POD was selected from a chronic/carcinogenicity study in rats based on body weight effects. Short and intermediate-term incidental oral, dermal and inhalation PODs were selected from an oral rat reproduction study based on decreased body weight effects in pups and parental animals. A dermal absorption factor is applied when dermal exposure endpoints are selected from oral toxicity studies. A dermal absorption factor of 6% was used for the dermal exposure assessment. Inhalation toxicity is assumed to be equivalent to oral toxicity. An uncertainty factor of 100X was applied endpoints selected for all exposures routes (10X for interspecies extrapolation, 10X for intraspecies variation).

Exposure/Risk Assessment and Risk Characterization

Risk assessments were conducted for dietary (food and water), occupational and aggregate exposure for the proposed new uses of difenoconazole. A new residential assessment is not required because the proposed new use does not include residential applications or exposures. Screening level acute and refined chronic dietary and drinking water risk assessments indicate that for all commodities, dietary and drinking water exposure estimates are below HED's level of concern. Additionally, the requested uses of difenoconazole resulted in an increase in dietary exposure estimates for free triazole or conjugated triazoles. Therefore, dietary exposure analyses for the triazole metabolites needed to be updated (T. Morton, D397591, 1/26/12).Risk estimates for worker handler and post-application exposure scenarios exposures are not of concern at maximum use rates for existing and proposed new uses. Aggregate risks are not of concern.

Aggregate Assessment of Free Triazole & its Conjugates

The addition of the new proposed uses increases the aggregate exposure to free triazoles and its conjugates. Therefore, the aggregate human health risk assessment was updated for free triazoles and its conjugates and the aggregate estimates remain below HED's level of concern.

Use of Human Studies

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, listed in Appendix D have been determined to require a review of their ethical conduct. Some of these studies are also subject to review by the Human Studies Review Board. All of the studies used have received the appropriate review.

2.0 HED RECOMMENDATIONS

2.1 Data Deficiencies

Submission of a revised Section B and a revised Section F are required (see Section 2.2.3). An immunotoxicity study, required under Part 158 Toxicology Data requirements, has been submitted and is under review. The Hazard and Science Policy Council (HASPOC) concluded based on a weight of evidence (WOE) approach that a 28-day inhalation toxicity study is not required at this time. This approach considered all of the available hazard and exposure information for difenoconazole, including: (1) the use of an oral POD that results in MOEs greater than 1,300 (the lowest MOE) for risk via the inhalation route resulting from occupational and residential; (2) the physical/chemical properties and very low vapor pressure of difenoconazole; and (3) the toxicological profile of difenoconazole.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

An adequate enforcement method, GC/NPD method AG-575B, is available for the determination of residues of difenoconazole *per se* in/on plant commodities. An adequate enforcement method, LC/MS/MS method REM 147.07b, is available for the determination of residues of difenoconazole and CGA-205375 in livestock commodities. Adequate confirmatory methods are also available.

2.2.2 International Harmonization

Codex maximum residue levels (MRLs) for residues of difenoconazole *per se* have been established at 0.5 ppm for tomato; 0.5 ppm for pome fruits; and 0.02 ppm for potato. Based on the available magnitude of the residue data, harmonization with these established Codex MRLs is not possible because, due to differences in good agricultural practices (GAP) the Codex MRLs are too low to adequately cover residues resulting from the proposed use rates in the U.S. Mexican and Canadian MRLs have been established for difenoconazole; however, no Mexican MRLs have been established for the requested crops. Canadian MRLs for residues of difenoconazole *per se* have been established at 0.6 ppm for a number of fruiting vegetables and 1.0 ppm for a number of pome fruit, and are in harmony with proposed U.S. tolerances. HED has been informed by RD that Canada has agreed to harmonize with the proposed U.S. tolerance for vegetable, tuberous and corm, subgroup 1C at 4.0 ppm.

2.2.3 Recommended Tolerances

HED has examined the residue chemistry database for difenoconazole and pending submission of a revised Section F (see requirements under Revisions to Petitioned for Tolerances), there are no residue chemistry issues that would preclude establishment of tolerances for residues of difenoconazole only in/on the commodities listed below:

Vegetable, fruiting, group 8-10 .....0.60 ppm
Fruit, citrus, group 10-10 .....0.60 ppm
Fruit, pome, group 11-10 .....1.0 ppm
Berry, low growing, subgroup 13-07G, except cranberry .....2.5 ppm
Vegetable, tuberous and corm, subgroup 1C .....4.0 ppm
Potato, wet peel .....7.3 ppm

Currently established tolerances for residues of difenoconazole in/on Vegetable, fruiting, group 8 (0.60 ppm); Fruit, citrus, group 10 (0.60 ppm); Fruit, pome group 11 (1.0 ppm); and Strawberry (2.5 ppm) should be removed.

Notes to PM:

1. A tolerance for Low growing berry subgroup 13-07G, except cranberry was specified in the Notice of Filing. Available data would support a tolerance in/on Berry, low growing, subgroup 13-07G. The petition is unclear as to why the petitioner wants to restrict the use on cranberry.

2. As directed by RD, the proposed use on Grapes and other small fruit vine climbing subgroup (except fuzzy kiwifruit) was not considered because the Notice of Filing did not include a tolerance proposal for this subgroup.

3. No data were submitted to address existing residue chemistry conditions of registration for the end-use products under consideration. Although not reiterated here, these data remain outstanding and are relevant to the current petition.

4. Use information was taken from Section B of the petition only. No additional draft labeling was provided for review. RD informed HED that the petitioner is requesting a postharvest use on all commodities listed under Vegetables, tuberous and corm, subgroup 1C and not just potato as specified in Section B of the petition.

2.2.4 Revisions to Petitioned-For Tolerances

HED's recommended revisions to the tolerances and/or commodity definitions submitted by IR-4 for this Section 3 petition are listed in Table 1. The proposed removal of the currently established tolerance for residues of difenoconazole on potato, processed waste is not appropriate; a tolerance is needed for residues of difenoconazole in potato, wet peel at 7.3 ppm.

Table 1. Tolerance Summary for Difenoconazole.

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	*Correct Commodity Definition;* Comments
Vegetable, fruiting, group 8-10	0.6	0.60	
Fruit, citrus, group 10-10	0.6	0.60	
Fruit, pome, group 11-10	1.0	1.0	
Low growing berry subgroup 13-07G, except cranberry	2.5	2.5	*Berry, low growing, subgroup 13-07G, except cranberry*
Vegetable, tuberous and corm, subgroup 1C	4.0	4.0	
Potatoes, processed waste	remove	7.3	*Potato, wet peel*
Vegetable, fruiting, group 8	remove	remove	
Fruit, citrus, group 10	remove	remove	
Fruit, pome, group 11	remove	remove	
Strawberry	remove	remove	

2.2.5 Label Recommendations

- For Inspire™ Fungicide, Section B of the petition must be amended to: remove the restriction for use on small tomatoes (page 25 of 68); and remove all use directions for grapes and other small fruit vine climbing except fuzzy kiwifruit (page 26 of 68).

- For Inspire™ XT Fungicide, Section B of the petition must be amended to: remove all use directions for bulb vegetables (page 41 of 68).

- For Quadris Top™ Fungicide, Section B of the petition must be amended to: remove the restriction for use on small tomatoes (page 39 of 68); and remove all use directions for grapes and other small fruit vine climbing except fuzzy kiwifruit (page 36 of 68).

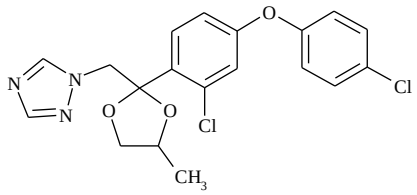
- For Inspire Super™ Fungicide, Section B of the petition must be amended to: remove the restriction for use on small tomatoes (page 30 of 68); and remove all use directions for grapes and other small fruit vine climbing except fuzzy kiwifruit (page 31 of 68).

- For Thesis™ Fungicide, Section B of the petition must be amended to: specify a maximum use rate of 0.0070 lb ai/ton of tubers (not just 0.3 fl. oz. product/ton of tubers); specify a delivery rate of 0.5 gal/ton of tubers; prohibit the use of adjuvants; and specify use on all tuberous and corm vegetables listed under subgroup 1C. . RD informed HED that the petitioner is requesting a postharvest use on all commodities listed under Vegetables, tuberous and corm, subgroup 1C and not just potato as specified in Section B of the petition.

- Concerning rotational crop restrictions and foliar uses under consideration: Although no information was provided on this topic in Section B of the petition, HED has determined that available data support a 30-day plantback interval (PBI) for cereal and root/tuber crops not already registered for foliar use with difenoconazole and a 60-day PBI for all other crops not already registered for foliar use with difenoconazole.

3.0 INGREDIENT PROFILE

3.1 Chemical Identity

Table 2. Structures and Nomenclature.	
Chemical structure of difenoconazole	
Common name	Difenoconazole
Company experimental name	CGA-169374
IUPAC name	1-({2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-yl}methyl)-1H-1,2,4-triazole
CAS name	1-[[2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole
CAS registry number	119446-68-3
End-use products (EP)	Inspire™ Fungicide (100-1262), Inspire™ XT Fungicide (100-1312), Quadris Top™ Fungicide (100-1313), Inspire Super™ Fungicide (100-1317), Thesis™ Fungicide (100-1386),

3.2 Physical/Chemical Characteristics

A detailed description of the physiochemical properties of difenoconazole is provided in Appendix C. Difenoconazole exhibits relatively low solubility in water and higher solubility in solvents. It has a very low vapor pressure. Based on the field and laboratory studies, difenoconazole is persistent in soil and slightly mobile. It has low potential to reach ground water, except in soils of high sand and low organic matter content. Difenoconazole does not present significant concerns for bioaccumulation based on the lipophilicity of the compound, as well as the mammalian metabolism studies.

3.3 Pesticide Use Pattern

Difenoconazole is currently registered in the U.S. for use as a seed treatment on barley, wheat, and triticale, canola, sweet corn and cotton. It is also registered for foliar applications to numerous fruit and vegetable crops, ornamentals and golf course turf. Proposed new uses include a post-harvest use on potato. The use patterns for the amended use are provided in Table 3.

Table 3. Summary of Proposed Amended Use for Difenoconazole.						
Appl. Timing, Type, and Equip.	**Formulation [EPA Reg. No.]**	**Max. Appl. Rate (AR) (lb ai/A)**	**Max. No. Appl. per Season**	**Max. Seasonal AR (lb ai/A)**	**PHI (days)**	**Use Directions and Limitations**
Potato PostHarvest (PH)						
In-line aqueous spray application using T-ject, CDA, or similar application system.	3.0 lb ai/gal FS [100-1386]	0.3 fl. oz of product/ton of tubers	1	N/A	N/A	For treatment of certain postharvest rots caused by Silver scurf (*Helminthosporium solani)* and *Fusium* species. Ensure proper coverage of the tubers. Tubers should be tumbling as they are treated. Mix the fungicide solution in an appropriate amount of water for the crop being treated. Must be used in tank mixture with fludioxonil and azoxystrobin.
Fruiting Vegetables						
Foliar, Broadcast, Ground, aerial, or chemigation	2.08 lb/gal EC [100-1262]	0.114	Not Specified (NS)	0.46	0	A 7-day minimum RTI is specified. Do not use on varieties in which the mature tomatoes will be less than 2 inches (such as cherry tomatoes).
	1.05 lb/gal MAI SC [100-1313]	Peppers 0.115 Tomatoes 0.07				
	0.73 lb/gal MAI EW [100-1317]	0.114				
Citrus Fruits						
Foliar, Broadcast, Ground or aerial	2.08 lb/gal EC [100-1262]	0.125	NS	0.5	0	A 7-day minimum RTI is specified.
	1.05 lb/gal MAI SC [100-1313]	0.126				
Pome Fruits						
Foliar, Broadcast, Ground or aerial	2.08 lb/gal EC [100-1262]	0.07	NS	0.33	72 14	A 7-day minimum RTI is specified.
	0.73 lb/gal MAI EW [100-1317]	0.07				
Strawberries and other low growing berries (except cranberry)						
Foliar, Broadcast, Ground , aerial or chemigation	2.08 lb/gal EC [100-1262]	0.114	NS	0.46	0	A 7-day minimum RTI is specified.
	2.08 lb/gal MAI EC [100-1312]	0.114				
	1.05 lb/gal MAI SC	0.115				

Table 3. Summary of Proposed Amended Use for Difenoconazole.						
Appl. Timing, Type, and Equip.	**Formulation [EPA Reg. No.]**	**Max. Appl. Rate (AR) (lb ai/A)**	**Max. No. Appl. per Season**	**Max. Seasonal AR (lb ai/A)**	**PHI (days)**	**Use Directions and Limitations**
	[100-1313]					
	0.73 lb/gal MAI EW [100-1317]	0.114				

3.4 Anticipated Exposure Pathways

Dietary (food and water) and occupational exposures are expected based on existing and proposed new use difenoconazole as a post harvest use on potato. A new residential exposure assessment is not required because there are no residential uses or exposures associated with the proposed new use. The short-term aggregate exposure assessment, which takes into account residential exposure plus average exposure levels to food and water, has been updated to incorporate dietary exposure from the proposed new uses.

3.5 Considerations of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post application are evaluated. Further considerations are currently in development, as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 HAZARD CHARACTERIZATION/ASSESSMENT

4.1 Toxicology Studies Available for Analysis

The toxicology database for difenoconazole is adequate for evaluating and characterizing difenoconazole toxicity and selecting endpoints for purposes of this risk assessment. All toxicity studies required in accordance with new 40 CFR Part 158 the data requirements have been submitted. An immunotoxicity study has been submitted and is under review.

4.2 Absorption, Distribution, Metabolism and Excretion

The absorption, distribution, metabolism, and excretion of difenoconazole were studied in rats. In one study, the test compound was labeled with C^{14} at either the phenyl or triazole ring. Animals were administered a single oral gavage dose of 0.5 or 300 mg/kg of radiolabeled compound or 0.5 mg/kg unlabeled compound by gavage for 14 days followed by a single gavage dose of 0.5 mg/kg [^{14}C]-difenoconazole on day 15. In a second follow-up study [^{14}C]-difenoconazole (phenyl ring label) was administered as single oral gavage dose of 0.5 or 300 mg/kg. The second study was conducted to address deficiencies in the initial study by providing biliary excretion and identification of metabolites.

Difenoconazole was rapidly absorbed and extensively distributed, metabolized, and excreted in rats for all dosing regimens. Distribution, metabolism and elimination of difenoconazole were not sex related in the first study. Recovery of administered dose was 96-108%. Biliary excretion, examined in the second study, constituted the main route of elimination with some dose and sex dependency (75% at the low dose for both sexes; 56% for males and 39% for females at the high dose). Urinary and fecal eliminations exhibited a dose-related pattern at 48 hours. In bile duct cannulated rats, 9-l4% of dose was eliminated in the urine at the low dose versus 1% in the high-dose rats. In bile duct cannulated rats, 2-4% was eliminated in the feces at the low dose versus 17-22% at the high dose. Half-lives of elimination are approximately 20 hours for the low dose groups and 33-48 hours for the high dose group. Radioactivity in the blood peaked at 2 to 4 hours at the low and high dose respectively.

Difenoconazole undergoes successive oxidation and conjugation reactions. Following administration of 300 mg/kg of (^{14}C-phenyl) difenoconazole, three major urinary metabolites were identified as CGA 205375 and HO-CGA 205375 (6% of dose), sulfate conjugates (and their isomers) of HO-205375 (3.9% of dose), and the hydroxyacetic metabolite of HO-CGA 205375 (2.0% of dose). No single unknown urinary metabolite accounted for >1.1% of the dose. Free triazole metabolite was detected in the urine of the triazole-label groups and its byproduct was detected in the liver of phenyl labeled groups only.

The study results indicate that difenoconazole and/or its metabolites do not bioaccumulate appreciably following oral exposure since all tissues contained negligible levels (<1%) or radioactivity 7 days post exposure.

A dermal absorption factor of 6% was derived based on data from a triple pack of a 28 rat *in vivo* dermal absorption study and *in vitro* dermal absorption studies conducted with rat and human skin. Inhalation toxicity is assumed to be equivalent to oral toxicity.

4.3 Toxicological Effects

Subchronic and chronic studies with difenoconazole in mice and rats showed decreased body weights, decreased body weight gains and effects on the liver (e.g. hepatocellular hypertrophy, liver necrosis, fatty changes in the liver). In an acute neurotoxicity study in rats, reduced fore-limb grip strength was observed on day 1 in males and clinical signs of neurotoxicity were observed in females at the limit dose of 2000 mg/kg. In a subchronic

neurotoxicity study in rats, decreased hind limb strength was observed in males only at the mid- and high-doses. However, the effects observed in acute and subchronic neurotoxicity studies are transient, and the dose-response is well characterized with identified no observed adverse effect levels (NOAELs). No systemic toxicity was observed at the limit dose in the most recently submitted 28-day rat dermal toxicity study.

The available toxicity studies indicated no increased susceptibility of rats or rabbits from *in utero* or postnatal exposure to difenoconazole. In prenatal developmental toxicity studies in rats and rabbits and in the two-generation reproduction study in rats, fetal/offspring toxicity, when observed, occurred at equivalent or higher doses than in the maternal/parental animals.

There are no indications in the available studies that organs associated with immune function, such as the thymus and spleen, are affected by difenoconazole. An immunotoxicity study, required under Part 158 Toxicology Data requirements, has been submitted and is under review.

In accordance with HED's current policy and EPA's 2005 Cancer Guidelines, difenoconazole is classified as "Suggestive Evidence of Carcinogenic Potential" based on liver tumors observed in mice at 300 ppm and higher, the absence of tumors at two lower doses of 10 and 30 ppm, excessive toxicity observed at the two highest doses of 2500 and 4500 ppm, the absence of genotoxic and no evidence of carcinogenicity in rats. HED's Cancer Peer Review Committee recommended use of an MOE approach to risk assessment using the chronic point of departure (POD) based on effects observed in the chronic mouse study relevant to tumor development (*i.e.*, hepatocellular hypertrophy, liver necrosis, fatty changes in the liver and bile stasis). The POD is considered protective of the cancer effects.

Difenoconazole possesses low acute toxicity by the oral, dermal and inhalation routes of exposure. It is not an eye or skin irritant and is not a sensitizer.

The toxicity profiles for difenoconazole are provided in Appendix A.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)

The FQPA factor for increased susceptibility to infants and children is reduced to 1x based on the following considerations. Further discussion may be found in the following sections.

- The toxicology data base for difenoconazole is complete and adequate for assessing increased susceptibility under FQPA.
- There is no indication of increased susceptibility of rats or rabbit fetuses to in utero and/or postnatal exposure in the developmental and reproductive toxicity data.
- There are no residual uncertainties in the exposure database.
- The dietary risk assessment is conservative and will not underestimate dietary exposure to difenoconazole.

4.4.1 Completeness of the Toxicology Database

The toxicity database is sufficient for a full hazard evaluation and is considered adequate to evaluate risks to infants and children. Acceptable acute and subchronic neurotoxicity studies are available. An immunotoxicity study required under new 40 CFR Part 158 data requirements for registration of a pesticide (food and non-food uses) has been submitted and is under review. The Hazard and Science Policy Council (HASPOC) concluded based on a weight of evidence (WOE) approach that a 28-day inhalation toxicity study is not required at this time. This approach considered all of the available hazard and exposure information for difenoconazole, including: (1) the use of an oral POD that results in MOEs greater than 1,300 (the lowest MOE) for risk via the inhalation route resulting from occupational and residential; (2) the physical/chemical properties and very low vapor pressure of difenoconazole; and (3) the toxicological profile of difenoconazole.

4.4.2 Evidence of Neurotoxicity

In an acute neurotoxicity study in rats, reduced fore-limb grip strength was observed on day 1 in males. Clinical signs of neurotoxicity were observed in females at the limit dose of 2000 mg/kg. The effect in males is considered transient since it was not observed at later observation points. Toxicity in females was observed only at the limit dose. In a subchronic neurotoxicity study in rats decreased hind limb strength was observed in males only. The effects observed in acute and subchronic neurotoxicity studies are transient, and the dose-response is well characterized with identified NOAELs. Based on the toxicity profile, and lack of concern for neurotoxicity, a developmental neurotoxicity study in rats is not required.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

The available Agency Guideline studies indicated no increased susceptibility of rats or rabbits to in utero and/or postnatal exposure to difenoconazole. In the prenatal developmental toxicity studies in rats and rabbits and the two-generation reproduction study in rats, toxicity to the fetuses/offspring, when observed, occurred at equivalent or higher doses than in the maternal/parental animals.

In a rat developmental toxicity study developmental effects were observed at doses higher than those which caused maternal toxicity. Developmental effects in the rat included increased incidence ossification of the thoracic vertebrae and hyoid, decreased number of sternal centers of ossification, increased number of ribs and thoracic vertebrae, and decreased number of lumbar vertebrae. In the rabbit study, developmental effects (increases in post-implantation loss and resorptions and decreases in fetal body weight) were also seen at maternally toxic doses. In the two-generation reproduction study in rats, toxicity to the fetuses/offspring, when observed, occurred at equivalent or higher doses than in the maternal/parental animals.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties in the exposure database. The dietary risk assessment is conservative and will not underestimate dietary exposure to difenoconazole.

4.5 Toxicity Endpoint and Point of Departure

4.5.1 Dose-Response Assessment

Toxicity endpoints and points of departure (PODs) for dietary (food and water), occupational, and residential exposure scenarios are summarized below. A detailed description of the studies used as a basis for the selected endpoints are presented in Appendix A.

An acute POD of 25 mg/kg/day (NOAEL) was selected from an acute neurotoxicity study in rats based on reduced fore-limb grip strength in males on day 1 at the LOAEL of 200 mg/kg/day. An uncertainty factor (UF) of 100x (10x to account for interspecies extrapolation and 10x for intraspecies variation) was applied to the NOAEL to obtain an acute reference dose (aRfD) of 1.0 mg/kg/day. Since the FQPA factor has been reduced to 1X, the acute population adjusted dose (aPAD) is equivalent to the aRfD. The selected endpoint is considered appropriate for acute dietary exposure because effects were seen after a single dose. The endpoint is protective of the general population and all subpopulations for effects seen in the acute neurotoxicity study in rats. It is also protective of developmental and maternal effects observed in the rabbit developmental toxicity study at the LOAEL of 75 mg/kg/day and NOAEL of 25 mg/kg/day.

A chronic POD of 0.96 mg/kg/day (NOAEL) was selected from a chronic/oncogenicity oral study in rats based on cumulative decreases in body weight gains in males observed at the LOAEL of 24 mg/kg/day. A UF of 100x (10x to account for interspecies extrapolation and 10x for intraspecies variation) was applied to the dose to obtain a chronic reference dose (cRfD/cPAD) of 0.01 mg/kg/day.

Short-term incidental oral and short- and intermediate term dermal and inhalation PODs of 1.25 mg/kg/day were selected from a two generation reproduction study in rats based on decreased pup weight in males at 12.5 mg/kg/day (LOAEL) on day 21, and reductions in body weight gain in F0 females. Although dermal toxicity studies are available, a POD from an oral study was selected because effects in young animals (decreased pup weight) the primary effect of concern for short, intermediate and long term exposure is not specifically evaluated in the available dermal toxicity studies that only assess adult animals. The selected endpoint is protective of offspring effects from dermal exposure. An MOE 100 is required for the short- and intermediate-term dermal and inhalation exposure scenarios based on the conventional uncertainty factor of 100 (10x for interspecies extrapolation and 10x for intraspecies variation). There are no residential uses for difenoconazole that would result in incidental oral exposure to children.

A dermal absorption factor (DAF) is applied when dermal exposure endpoints are selected from oral toxicity studies. The dermal factor converts the oral dose to an equivalent

dermal dose for the risk assessment. A DAF of 6% was selected for use in risk assessment based on available in vivo dermal absorption studies in rat and in vitro dermal absorption studies conducted with rat and human skin. Further discussion of the dermal absorption may be found in Attachment A.3.

4.5.2 Recommendations for Combining Exposure Routes

When there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. Oral, dermal and inhalation exposures to residents should be aggregated for difenoconazole because the endpoints selected for these exposure routes are based on common toxicological effects.

4.5.3 Classification of Carcinogenic Potential

Difenoconazole is not mutagenic, and no evidence of carcinogenicity was seen in rats. Evidence for carcinogenicity was seen in mice, where liver tumors were induced at doses which were considered to be excessively high for carcinogenicity testing. Liver tumors were observed in mice at 300 ppm and higher; however, based on excessive toxicity observed at the two highest doses of 2500 and 4500 ppm (females terminated after two weeks due to excessive toxicity resulting in moribundity and death), the absence of tumors at two lower doses of 10 and 30 ppm, the absence of genotoxic effects, and no evidence of carcinogenicity in rats. In accordance with HED's current policy and EPA's 2005 Cancer Guidelines, difenoconazole is classified as "Suggestive Evidence of Carcinogenic Potential," based on excessive toxicity observed at the two highest doses, the absence of tumors at the lower doses and the absence of genotoxic effects. Based on the CPRC recommendation, the risk assessment uses an (MOE) approach utilizing the no-observable-adverse-effects-level (NOAEL) of 30 ppm (4.7 and 5.6 mg/kg/day in males and females, respectively) and the lowest-observable-adverse-effects-level (LOAEL) of 300 ppm (46 and 58 mg/kg/day in males and females, respectively) from the mouse study using only those biological endpoints which were relevant to tumor development (*i.e.*, hepatocellular hypertrophy, liver necrosis, fatty changes in the liver and bile stasis). The chronic POD of 0.96 mg/kg/day selected based on bodyweight effects is protective of the cancer effects.

4.5.4 Summary of Points of Departure Used in Risk Assessment

Toxicological doses/endpoints selected for the difenoconazole risk assessment are provided in Tables 4 and 5.

Table 4. Summary of Toxicological Doses and Endpoints for Difenoconazole for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, LOC for Risk Assessment**	**Study and Relevant Toxicological Effects**
Acute Dietary (All populations)	NOAEL = 25 mg/kg	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	aRfD = aPAD = 0.25 mg/kg/day	Acute Neurotoxicity Study in Rats LOAEL= 200 mg/kg in males based on reduced fore-limb grip strength in males on day 1.
Chronic Dietary (All populations)	NOAEL = 0.96 mg/kg/day	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	cRfD = cPAD = 0.01mg/kg/day	Combined chronic toxicity/carcinogenicity (rat; dietary) LOAEL = 24.1/32.8 mg/kg/day (M/F) based on cumulative decreases in body-weight gains.
Incidental Oral Short-Term (1-30 days)	Oral NOAEL = 1.25 mg/kg/day	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	Residential LOC for MOE<100	Reproduction and fertility Study (rat; dietary) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 and reduction in body-weight gain of F_0 females prior to mating, gestation and lactation.
Dermal Short- and Intermediate- Term (1-30 days and 1-6 months) DAF = 6%	Oral NOAEL = 1.25 mg/kg/day	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	Residential LOC for MOE<100	Reproduction and fertility Study (rat; dietary) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 and reduction in body-weight gain of F_0 females prior to mating, gestation and lactation.
Inhalation (Short- and Intermediate-term) Inhalation and oral absorption assumed equivalent	Oral NOAEL = 1.25 mg/kg/day	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	Residential LOC for MOE<100	Reproduction and fertility Study (rat; dietary) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 and reduction in body-weight gain of F_0 females prior to mating, gestation and lactation.
Cancer (oral, dermal, inhalation)	Difenoconazole is classified "Suggestive Evidence of Carcinogenic Potential" with a non-linear (MOE) approach for human risk characterization (CPRC Document, 7/27/94, Memo, P. V. Shah dated March 3, 2007, HED Doc. No. 0054532).			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies DAF = Dermal Absorption Factor

Table 5. Summary of Toxicological Doses and Endpoints for Difenoconazole for Use Occupational Human Health Risk Assessments				
Exposure Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short- and Intermediate- Term (1-30 days and 1-6 months) DAF = 6%	Oral NOAEL = 1.25 mg/kg/day	UF_A = 10X UF_H = 10X	Occupational LOC for MOE<100	Reproduction and fertility Study (rat; dietary) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 and reduction in body-weight gain of F_0 females prior to mating, gestation and lactation.
Inhalation (Short- and Intermediate-term) Inhalation and oral absorption assumed equivalent	Oral NOAEL = 1.25 mg/kg/day	UF_A = 10X UF_H = 10X	Occupational LOC for MOE<100	Reproduction and fertility Study (rat; dietary) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 and reduction in body-weight gain of F_0 females prior to mating, gestation and lactation.
Cancer (oral, dermal, inhalation)	Difenoconazole is classified "Suggestive Evidence of Carcinogenic Potential" with a non-linear (MOE) approach for human risk characterization (CPRC Document, 7/27/94, Memo, P. V. Shah dated March 3, 2007, HED Doc. No. 0054532).			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

5.0 DIETARY AND DRINKING WATER EXPOSURE AND RISK ASSESSMENT

5.1 Metabolite/Degradate Residue Profile

5.1.1 Summary of Plant and Animal Metabolism Studies

The nature of the residue in plants is understood based on acceptable plant metabolism studies reflecting foliar applications in canola, grape, potato, tomato, and wheat, and seed treatment in wheat. HED concludes that the residue of concern for both tolerance enforcement and risk assessment for crops included in this petition is difenoconazole *per se*. The nature of the residue in livestock is understood based on acceptable goat and hen metabolism studies. The residues of concern for both tolerance setting and risk assessment for livestock commodities are difenoconazole *per se* and its metabolite CGA-205375. In addition, metabolite OH-CGA-169374, which comprised 15% of the TRR in goat milk from the phenyl-labeled study, should be considered as a residue of concern for the dietary risk assessment.

The nature of the residue in rotational crops is adequately understood. The metabolism of difenoconazole in rotational crops is similar to that of primary crops. The available difenoconazole confined and limited field rotational crop trials are deemed adequate to satisfy data requirements under Guidelines 860.1850 and 860.1900. Taken together, these data support a 30-day plantback interval (PBI) for cereal and root/tuber crops not already registered for foliar use with difenoconazole and a 60-day PBI for all other crops not already registered for foliar use

with difenoconazole. With these PBIs, tolerances for residues of difenoconazole are not needed for rotational crops.

5.1.2 Comparison of Metabolic Pathways

Little information is available on the toxicity of the major difenoconazole metabolites. The CGA-205375 metabolite formed in livestock appears to be formed in the rat also and is, therefore, part of the total toxic exposure for these animals.

5.1.3 Residues of Concern Summary and Rationale

Residues of concern were determined based on recommendations from the HED Residues of Concern Knowledgebase Sub-committee (ROCKS) (D391350, 9/19/11). The residue of concern for plant commodities for tolerance expression and risk assessment purposes is difenoconazole *per se*. The HED ROCKS has determined that the parent compound and the CGA-205375 metabolite are the residues of concern in livestock commodities for both the tolerance expression and the risk assessment. In addition, metabolite OH-CGA-169374, which comprised 15% of the TRR in goat milk from the phenyl-labeled study, should be considered as a residue of concern for the dietary risk assessment. Based on available goat metabolism data, total residues of concern in milk for dietary risk assessments (parent, CGA-205375, and OH-CGA-169374), should be calculated by multiplying the tolerance in milk by a factor of 1.5x. Table 6 summarizes tolerance expression and the residues of concern in plant and livestock commodities.

Table 6. Difenoconazole Residues of Concern in Plants and Ruminants.

Matrix		Residues of Concern	
		For Risk Assessment	**For Tolerance Expression**
Plants	Primary and Rotational crops	Parent Only	Parent Only
Livestock	Ruminant and Poultry	Parent and CGA 205375	Parent and CGA 205375
	Milk	Parent, CGA 205375 and OH-CGA-169374	Parent and CGA 205375
Drinking Water		Parent and CGA 205375	NA

Note: The triazole-containing metabolites 1,2,4-T, TA, and TAA should be included in the residues of concern for risk assessment purposes only for plant and livestock commodities. Since these metabolites are common to the entire class of traizole-derivative fungicides and because of differential toxicity between metabolites and the various parent compounds, risks associated with exposure to 1,2,4-T and to TA/TAA are addressed separately.

5.2 Food Residue Profile

5.2.1 Residues in Crops

The submitted postharvest potato magnitude of the residue data, conducted with a 3.0 lb/gal flowable suspension (FS) formulation of difenoconazole adequately reflect the proposed use pattern for potato postharvest. Provided the use is expanded to all tuber and corm vegetables listed under subgroup 1C, for which potato is the representative commodity, these data will support a tolerance of 4.0 ppm in/on Vegetables, tuberous and corm, subgroup 1C.

Previously submitted field trial data are adequate to support the proposed amended uses. It is important to note that the proposed amendments to existing labels are limited to expansions to add the commodities specified under the new crop groups/subgroups and do not include substantive changes to currently registered use patterns (i.e., maximum use rates, retreatment intervals, preharvest intervals, use of adjuvants, etc.). The proposed tolerances in/on Fruiting Vegetables Group 8-10 (0.6 ppm); Citrus Fruits Group 10-10 (0.6 ppm), Pome Fruits Group 11-10 (1.0 ppm), and Low growing Berry Subgroup 13-07G, Except Cranberry (2.5 ppm) are appropriate.

5.2.2 Residue in Livestock and Poultry

There are no new livestock feedstuffs associated with the proposed uses since difenoconazole is already registered for foliar uses on potatoes, citrus fruits, and pome fruits. However, due to the proposed postharvest use on potatoes, difenoconazole residue estimates in/on potato culls and potato processing waste, which are beef and dairy feedstuffs, have increased substantially. Potato culls and potato processing waste are both carbohydrate concentrates which are sometimes used in cattle feeding and considered alternative feedstuffs. There are no poultry or swine feedstuffs associated with the proposed uses. Adequate cattle and poultry feeding studies are available for difenoconazole.

The dietary burdens for beef and dairy cattle are recalculated for this Section 3 action. In accordance with ChemSAC recommendations concerning blended commodities (ChemSAC meeting minutes 12/21/11), the difenoconazole residue estimate in/on potato processing waste for livestock MRBD calculations (3.5 ppm) was based on the median residue value for potato reflecting the proposed post harvest use (1.13 ppm) and the average concentration factor for potato wet peel (3.1x). Potato processing waste replaces AGF and wet apple pomace as the major contributors to the MRBDs of cattle for difenoconazole. The MRBDs are recalculated to be: 7.4 ppm for beef cattle and 2.8 ppm for dairy cattle. Based on the recalculated dietary burdens and the feeding study data, HED concludes that the currently established tolerances for milk, meat, fat, meat byproducts (except liver) and liver are adequate to support the proposed uses.

5.2.3 Residues in Processed Commodities

Adequate processing data for potato were submitted with the petition. The potato processing data indicate that residues of difenoconazole do not concentrate in flakes and chips but do concentrate in wet peel. Based on the HAFT for residues in/on potatoes postharvest (2.34 ppm) and the average processing factor for potato wet peel (3.1x), expected residues of difenoconazole from the proposed postharvest use on potato would be 7.3 ppm in potato, peel, wet. The proposed removal of the currently established tolerance for residues of difenoconazole on potato, processed waste is not appropriate; a tolerance is needed for residues of difenoconazole in potato, peel, wet at 7.3 ppm. Apple, tomato, and orange processing data were previously submitted and are adequate to support the proposed uses. No changes to the currently established tolerances in apple, wet pomace (4.5 ppm), citrus, dried pulp (2.0 ppm), and citrus oil (25 ppm) are needed.

5.3 Water Residue Profile

The drinking water estimates used in the dietary risk assessment were provided by the Environmental Fate and Effects Division. EFED conducted a Tier II drinking water assessment for surface water sources using the Pesticide Root Zone/Exposure Analysis Modeling System (PRZM/EXAMS) for the registered and proposed new uses. Among the registered and proposed new uses, the highest estimated drinking water concentrations (EDWCs) for surface water sources were derived for aerial applications of difenoconazole to New York grapes at the maximum annual application rate of 0.46 lb ai/acre The estimated drinking water residues for 1-in-10 year annual peak, 1-in-10 year annual mean, and 36-year annual mean are 17.4, 11.8, and 8.6 µg/L (ppb) respectively. The highest Screening Concentration In GROund Water (SCI-GROW) estimated drinking water concentration of difenoconazole from shallow ground water sources is 1.28×10^{-2} µg/L, obtained for the maximum application rate for ornamentals (0.52 lb ai/A). These concentrations can be considered as both the acute and chronic groundwater values. The EDWCs from ground water sources are expected to be the same for the proposed golf course turf uses as estimated for ornamentals. The 1-in-10 year annual peak EDWC of 17.4 µg/L (ppb) was used for the acute dietary (food plus water) exposure analysis and the 1-in-10 year annual mean EDWC of 11.8 µg/L (ppb) was used for the chronic dietary (food plus water) exposure analysis.

5.4 Dietary and Drinking Water Exposure and Risk

Screening level acute and refined chronic dietary and drinking water exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model with the Food Commodity Intake Database (DEEM-FCID™). Dietary risk assessment incorporates both exposure and toxicity of a given pesticide. For acute and chronic dietary assessments, the risk is expressed as a percentage of a maximum acceptable dose (i.e., the dose which HED has concluded will result in no unreasonable adverse health effects). This dose is referred to as the population adjusted dose (PAD). The PAD is equivalent to the POD divided by the uncertainty factors. For acute and non-cancer chronic exposures, HED is concerned when estimated dietary risk exceeds 100% of the PAD.

5.4.1 Acute Dietary Risk Assessment

The unrefined acute analysis for food and water assumed tolerance-level residues, 100% crop treated (CT), and the available empirical or DEEM™ (ver. 7.81) default processing factors. The resulting acute food plus water exposure estimates were less than HED's level of concern (-<100% of the acute population-adjusted dose (aPAD)) at the 95th percentile of the exposure distribution for the general U.S. population (12 % aPAD) and all population sub-groups; the most highly exposed population subgroup was children1-2 years old with 27 % aPAD.

Table 7. Summary of Acute Dietary Exposure (Food and Drinking Water) and Risk for Difenoconazole at the 95th Percentile.			
Population Subgroup	**aPAD (mg/kg/day)**	**Exposure (mg/kg/day)**	**%aPAD**
General U.S. Population	0.25	0.030385	12
All Infants (< 1 year old)		0.056767	23
Children 1-2 years old		**0.066505**	**27**
Children 3-5 years old		0.053081	21
Children 6-12 years old		0.034395	14
Youth 13-19 years old		0.023787	10
Adults 20-49 years old		0.022687	9
Adults 50+ years old		0.025302	10
Females 13-49 years old		0.022729	9

5.4.2 Chronic Dietary Risk Assessment

The somewhat refined chronic analysis for food and water assumed tolerance-level residues for some commodities, average field trial residues for the majority of commodities, the available empirical or DEEM™ (ver. 7.81) default processing factors, and 100 % CT. The resulting chronic food plus water exposure estimates were less than HED's level of concern (-<100% of the chronic population-adjusted dose (cPAD)) for the general U.S. population (30 % cPAD) and all population sub-groups; the most highly exposed population subgroup was children 1 - 2 years old with 75 % cPAD.

Table 8. Summary of Chronic Dietary (Food and Drinking Water) Exposure and Risk for Difenoconazole.			
Population Subgroup	**cPAD (mg/kg/day)**	**Exposure (mg/kg/day)**	**%cPAD**
General U.S. Population	0.01	0.002987	30
All Infants (< 1 year old)		0.004701	47
Children 1-2 years old		**0.007460**	**75**
Children 3-5 years old		0.006242	62
Children 6-12 years old		0.003903	39
Youth 13-19 years old		0.002574	26
Adults 20-49 years old		0.002382	24
Adults 50+ years old		0.002594	26
Females 13-49 years old		0.002304	23

Dietary Assessment of Free Triazole and its Conjugates

Reference: *Common Triazole Metabolites: Updated Dietary (Food + Water) Exposure and Risk Assessment to Address The Amended Propiconazole Section 3 Registration to Add Uses on Snap beans, succulent shelled beans, dry beans, tomato (post-harvest, citrus (post-harvest), and stone fruit (post-harvest); The Amended Difenoconazole Section 3 Registration to Add Use on Root and Tuber group 1C; and the Amended Flutriafol Section 3 Registration to Add Use on Field Corn.T. Morton, DP397591.drs, 1/26/12.*

The proposed Section 3 uses of propiconazole results in an increase in dietary exposure estimates for free triazole or conjugated triazoles. Therefore, the last dietary exposure analyses for the triazole metabolites needed to be updated. The proposed Section 3 uses of difenoconazole results in dietary risk estimates below HED's level of concern; see Table 9.

Table 9. Summary of Dietary (Food and Drinking Water) Exposure and Risk for the Common Triazole Metabolites Adding the new Section 3 Uses for Propiconazole, Flutriafol, and Difenoconazole.

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% cPAD*	Dietary Exposure (mg/kg/day)	Risk
1,2,4-Triazole						
General U.S. Population	0.008892	30	0.001409	28	Not Applicable	Not Applicable
All Infants (< 1 year old)	0.012475	42	0.001923	39		
Children 1-2 years old	**0.023049**	**77**	**0.003723**	**75**		
Children 3-5 years old	0.017674	59	0.002994	60		
Children 6-12 years old	0.011632	39	0.001891	38		
Youth 13-19 years old	0.008196	27	0.001266	25		
Adults 20-49 years old	0.006959	23	0.001162	23		
Adults 50+ years old	0.006050	20	0.001097	22		
Females 13-49 years old	0.007007	23	0.001166	23		
Triazolylalanine + Triazolylacetic Acid						
General U.S. Population	Not Applicable	Not Applicable	0.019824	22	Not Applicable	Not Applicable
All Infants (< 1 year old)			0.020308	23		
Children 1-2 years old			**0.056263**	**63**		
Children 3-5 years old			0.045007	50		
Children 6-12 years old			0.028078	31		
Youth 13-19 years old			0.018635	21		
Adults 20-49 years old			0.015881	18		
Adults 50+ years old			0.014719	16		
Females 13-49 years old	**0.086155**	**86**	0.016036	18		

* The values for the highest exposed population for each type of risk assessment are bolded.

6.0 RESIDENTIAL EXPOSURE AND RISK

A new residential exposure assessment is not required for the proposed amended/new uses because there are no homeowner uses or application to residential areas associated with these uses. However, difenoconazole is registered on ornamentals and golf coarse turf which will result in residential exposure. Therefore, theses residential uses were aggregated with the recent dietary exposure.

6.1 Residential Bystander Post Application Inhalation Exposure

Based on the Agency's current practices, a quantitative residential bystander postapplication inhalation exposure assessment was not performed for difenoconazole at this time. However, volatilization of pesticides may be a potential source of postapplication inhalation exposure to individuals nearby to pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide,

Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009. The Agency received the SAP's final report on March 2, 2010 (http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html). The Agency is in the process of evaluating the SAP report and may, as appropriate, develop policies and procedures, to identify the need for and, subsequently, the way to incorporate postapplication inhalation exposure into the Agency's risk assessments. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative postapplication inhalation exposure assessment for difenoconazole.

6.2 Spray Drift

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for difenoconazole. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices (see the Agency's Spray Drift website for more information at http://www.epa.gov/opp00001/factsheets/spraydrift.htm). On a chemical by chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift.

7.0 AGGREGATE EXPOSURE AND RISK ASSESSMENT

In accordance with the FQPA, when there are potential residential exposures to a pesticide, aggregate risk assessment must consider exposures from three major routes: oral, dermal, and inhalation. There are three sources for these types of exposures: food, drinking water, and residential uses. In an aggregate assessment, risks from relevant sources are added together and compared to a level of concern. Since a common effect has been identified for assessment of short-term oral, dermal, and inhalation exposures (changes in body weights and body-weight gains) for difenoconazole, the short-term aggregate risk assessment combines exposure from food, water, and residential sources. Only short-term residential exposures are expected based on current use patterns. The acute and chronic exposure estimates from the dietary exposure analyses represent aggregate risk for acute and chronic exposures.

Difenoconazole is currently registered for the following uses that could result in residential exposures: Ornamentals. EPA assessed residential exposure using the following assumptions: Adults may be exposed to difenoconazole from its currently registered use on ornamentals. Residential pesticide handlers may be exposed to short-term duration (1 - 30 days) only. The dermal and inhalation (short-term) residential exposure was assessed for "homeowners" mixer/loader/applicator wearing short pants and short-sleeved shirts as well as

shoes plus socks using garden hose-end sprayer, "pump-up" compressed air sprayer, and backpack sprayer. Residential post-application exposure may occur from use of difenoconozole on golf course turf. Short-term dermal exposure was assessed for post-application exposure to golf course turf. Further information regarding EPA standard assumptions and generic inputs for residential exposures may be found at http://www.epa.gov/pesticides/trac/science/trac6a05.pdf.

7.1 Short-Term Aggregate Risk to Residential Applicators

Short term aggregate exposure takes into account residential exposure plus average exposure levels to food and water (considered to be a background exposure level). The short term aggregate risk for residential handlers is the estimated risk associated with combined risks from average food and drinking water exposures and dermal and inhalation exposures to adult applicators. Short term aggregate risk estimates for residential handlers are provided in Table 10 aggregates the short-term risk for adults from residential handler exposure and average food and water exposure (as a background). The lowest aggregate MOE is 200, which is greater than the target MOE of 100 and therefore not of concern.

Table 10: Estimated Difenoconazole Short-term Aggregate Risk to Adults from Residential Handler Activities

Exposure Scenario	Target MOE[1]	Route of Exposure	Daily dose mg/kg/day	NOAELs mg/kg/day	MOE at Day 0	Combined MOE[4]
Average Food and Water (As background)	N/A	Food and water	0.002958	1.25	420 [2]	NA
Hose End Sprayer - Ornamentals	100	Dermal and Inhalation	0.0022		575 [3]	240
Handheld Pump Spray - Ornamentals			0.0031		400	200
Hose End Sprayer – Flower Gardens			0.0019		660	260
Handheld Pump Spray – Flower Gardens			0.0021		590	250

[1] Target MOE= 100, Developmental rat- increased incidence of rudimentary risks. NOAEL = 0.96
[2] MOE food and water = [(short-term oral NOAEL)/(chronic dietary exposure)]
[3] MOE dermal and inhalation = [(short -term NOAEL (1.25)/(high-end inhalation and dermal residential exposure)]
[4] Aggregate Combined MOE (food, water, and residential) = 1÷ [(1÷MOE food and water) + (1÷MOE handler inhalation and dermal)].

7.2 Short-Term Aggregate Risk for Residential Post-Application Exposure

Table 11 aggregates the short-term risk for adults from residential post application, and average food and water exposure. The highest post application exposure from residential use on turf was used in the short term aggregate. The aggregate MOE is 600, which is greater than the target MOE of 100. This aggregate exposure assessment is considered very conservative because the assumptions used for each of the scenarios separately are already high end (i.e., time spent outdoors, dislodgeable residues).

Table 11: Estimated Difenoconazole Short-term Aggregate Risk from Residential Post-Application Activities						
Exposure Scenario	**Target MOE[1]**	**Route of Exposure**	**Daily Dose mg/kg/day**	**NOAELs**	**MOE at Day 0**	**Combined MOE[4]**
Average Food and Water Adult	N/A	Food and water	0.002958	1.25	420 [2]	NA
Adult Golfer	100	Dermal	0.00024		5200 [3]	390

[1] Target MOE= 100, Developmental rat- increased incidence of rudimentary risks. NOAEL = 0.96
[2] MOE food and water = [(short-term oral NOAEL)/(chronic dietary exposure)]
[3] MOE dermal = [(short -term dermal NOAEL)/(high-end dermal residential exposure)]
[4] Aggregate Combined MOE (food, water, and residential) = 1÷ [(1÷MOE food and water) + (1÷MOE post appl. dermal)].

Updated Aggregate Assessment of Free Triazole & its Conjugates

Reference: *Common Triazole Metabolites: Updated Aggregate Human Health Risk Assessment to Address Tolerance Petitions for Propiconazole, Difenoconazole, and Flutriafol. DP397592, T. Morton, 1/26/12.*

The addition of the new proposed uses increase the aggregate exposure to free triazoles and its conjugates. Therefore, the aggregate human health risk assessment for free triazoles and its conjugates was updated and the aggregate estimates are below HED's level of concern (DP397592, T. Morton, 1/26/12).

8.0 CUMULATIVE RISK

Difenoconazole is a member of the triazole-containing class of pesticides. Although conazoles act similarly in plants (fungi) by inhibiting ergosterol biosynthesis, there is not necessarily a relationship between their pesticidal activity and their mechanism of toxicity in mammals. Structural similarities do not constitute a common mechanism of toxicity. Evidence is needed to establish that the chemicals operate by the same, or essentially the same, sequence of major biochemical events (EPA, 2002). In conazoles, however, a variable pattern of toxicological responses is found; some are hepatotoxic and hepatocarcinogenic in mice. Some induce thyroid tumors in rats. Some induce developmental, reproductive, and neurological effects in rodents. Furthermore, the conazoles produce a diverse range of biochemical events including altered cholesterol levels, stress responses, and altered DNA methylation. It is not clearly understood whether these biochemical events are directly connected to their toxicological outcomes. Thus, there is currently no evidence to indicate that conazoles share common mechanisms of toxicity and EPA is not following a cumulative risk approach based on a common mechanism of toxicity for the conazoles. For information regarding EPA's procedures for cumulating effects from substances found to have a common mechanism of toxicity, see EPA's website at http://www.epa.gov/pesticides/cumulative.

Difenoconazole is a triazole-derived pesticide. This class of compounds can form the common metabolite 1,2,4-triazole and two triazole conjugates (triazolylalanine and triazolylacetic acid). To support existing tolerances and to establish new tolerances for triazole-derivative pesticides, including propiconazole, U.S. EPA conducted a human health risk assessment for exposure to 1,2,4-triazole, triazolylalanine, and triazolylacetic acid resulting from the use of all current and

pending uses of any triazole-derived fungicide. The risk assessment is a highly conservative, screening-level evaluation in terms of hazards associated with common metabolites (e.g., use of a maximum combination of uncertainty factors) and potential dietary and non-dietary exposures (i.e., high end estimates of both dietary and non-dietary exposures). In addition, the Agency retained the additional 10X FQPA safety factor for the protection of infants and children. The assessment includes evaluations of risks for various subgroups, including those comprised of infants and children. The Agency's complete risk assessment is found in the propiconazole reregistration docket at http://www.regulations.gov, Docket Identification (ID) Number EPA-HQ-OPP-2005-0497.

9.0 OCCUPATIONAL EXPOSURE/RISK CHARACTERIZATION

Occupational handler and post-application exposure scenarios are assessed for the risk assessment of the uses. Based on the product labels and information provided by the registrant, short- and intermediate-term exposure is assessed for occupational handlers and post-application activities. Chronic exposure is not expected for the proposed use patterns. Dermal and inhalation exposures to workers are aggregated for difenoconazole because the PODs for these routes are based on common toxicological effects.

9.1 Handler Exposure

The term "handler" applies to individuals who mix, load, and apply the pesticide product. There is a potential for exposure to difenoconazole during mixing, loading, and application activities through inhalation routes only. Difenoconazole products are applied to using aerial, groundboom, chemigation, and handheld sprayers. The proposed new post harvest use on potatoes is by automated spray application.

9.1.1 Handler Exposure Scenarios

The following handler exposure scenarios evaluated for this assessment are based on information provided in the proposed labels.

9.2.1.1 Foliar Applications to Field Crops

- Open mixing/loading liquid formulation for groundboom, aerial, chemigation, and airblast application;
- Applying with aerial, groundboom, and airblast sprayer equipment; and
- Flagging for aerial application.

9.2.1.2 Post-Harvest Application to Potatoes

- Open mixing/loading liquid for automated spray application.

9.1.2 Handler Exposure Data and Assumptions

No chemical-specific handler exposure data were submitted in support of this registration. It is the policy of HED to use the best available data to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include the Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1), the Agricultural Handler Exposure Task Force (AHETF) database, the Outdoor Residential Exposure Task Force (ORETF) database, or other registrant-submitted occupational exposure studies. Some of these data are proprietary (e.g., AHETF data), and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures", are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (http://www.epa.gov/opp00001/science/handler-exposure-table.pdf), which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at http://www.epa.gov/pesticides/science/handler-exposure-data.html.

- Average body weight of an adult handler is 80 kg.
- Dermal absorption factor is 6%
- Exposure duration short-term (1- 30 days), intermediate-term (1-6 months)
- Maximum label application rates for aerial, groundboom and airblast to fruit, vegetable and berry crops:
  - 0.07 – 0.13 lb ai/A
- Area treated for aerial, groundboom, airblast and chemigation application to field crops:
  - 350 acres per day for aerial application
  - 80 acres per day for groundboom application
  - 40 acres per day for airblast application
- Maximum label application rates post-harvest use on potatoes
  - 0.00025 gal ai/lb potato
- Amount of potatoes treated/processed
  - 1,440,000 lbs per day (180,000 lbs per hour x 8 hrs per day)

9.1.3 Handler Exposure and Risk Estimates

All worker exposures are assessed as short- and intermediate-term based on label prescribed uses and expected exposure durations. Exposure and risk estimates indicate non-cancer risks are not of concern for occupational handler activities for the proposed new uses (MOEs > 100). A summary of occupational handler exposure and risk calculations, assumptions, and results are provided in Tables 12 and 13.

Table 12. Occupational Handler Short-/Intermediate-Term Dermal and Inhalation Exposure Estimated Risk										
Exposure Scenario	**Crop**	**Unit Exposure[1] (ug/lb ai)**		**App. Rate[2] (lb ai/A)**	**Area Treated[3] (A/Day)**	**ST & IT Dose (mg/kg/day)**		**ST & IT MOEs LOC = 100**		**Combined MOEs[8] LOC=100**
		Dermal Baseline	**Inhal BL**			**Dermal[4] Baseline**	**Inhal.[5] Baseline**	**Dermal[6] Baseline**	**Inhal.[7] Baseline**	**Inhal + Dermal**
Mixing/Loading – Liquid										
Groundboom	Citrus fruits	220	0.219	0.13	80	0.0017	0.000028	730	44,000	720
Airblast					40	0.00086	0.000014	1,500	88,000	1,400
Aerial & Chem.					350	0.0075	0.00012	170	10,000	160
Groundboom	Fruiting Vegetables; Strawberry/ low growing berry			0.11	80	0.0015	0.000024	860	52,000	850
Airblast					40	0.0007	0.000012	1,700	100,000	1,700
Aerial & Chem.					350	0.0064	0.00011	200	12,000	190
Groundboom	Pome Fruits			0.07	80	0.0009	0.000015	1,400	82,000	1,300
Airblast					40	0.0005	0.000008	2,700	160,000	2,700
Aerial & Chem.					350	0.0040	0.000067	310	19,000	300
Groundboom	Strawberry/ low growing berry			0.11	80	0.0015	0.000024	860	52,000	850
Airblast					40	0.0007	0.000012	1,700	100,000	1,700
Aerial & Chem.					350	0.0064	0.00011	200	12,000	190
Applying Liquid										
Groundboom	Citrus fruits	78.6	0.34	0.13	80	0.00061	0.000044	2,000	28,000	1,900
Airblast		1770	4.71		40	0.0069	0.00031	180	4,100	170
Aerial		N/A	0.068		350	N/A	0.000039	N/A	32,000	N/A
Groundboom	Fruiting Vegetables; Strawberry/ low growing berry	78.6	0.34	0.11	80	0.00052	0.000037	2,400	33,000	2,200
Airblast		1770	4.71		40	0.0058	0.00026	210	4,800	200
Aerial		N/A	0.068		350	N/A	0.000033	N/A	38,000	N/A
Groundboom	Pome Fruits	78.6	0.34	0.07	80	0.00033	0.000024	3,800	53,000	3,500
Airblast		1770	4.71		40	0.0037	0.00016	340	7,600	320
Aerial		N/A	0.068		350	N/A	0.000021	N/A	60,000	N/A
Groundboom	Strawberry/ low growing berry	78.6	0.34	0.11	80	0.00052	0.000037	2,400	33,000	2,200
Airblast		1770	4.71		40	0.0058	0.00026	210	4,800	200
Aerial		N/A	0.068		350	N/A	0.000033	N/A	38,000	N/A
Flagging										
Aerial	Citrus fruits	11	0.35	0.13	350	0.0063	0.00020	200	6,300	190
	Fruiting Vegetables; Strawberry/ low growing berry			0.11		0.0053	0.00017	240	7,400	230
	Pome Fruits			0.07		0.0034	0.00011	370	12,000	360

Table 12. Occupational Handler Short-/Intermediate-Term Dermal and Inhalation Exposure Estimated Risk										
Exposure Scenario	**Crop**	**Unit Exposure[1] (ug/lb ai)**		**App. Rate[2] (lb ai/A)**	**Area Treated[3] (A/Day)**	**ST & IT Dose (mg/kg/day)**		**ST & IT MOEs LOC = 100**		**Combined MOEs[8] LOC=100**
		Dermal Baseline	**Inhal BL**			**Dermal[4] Baseline**	**Inhal.[5] Baseline**	**Dermal[6] Baseline**	**Inhal.[7] Baseline**	**Inhal + Dermal**
	Strawberry/ low growing berry			0.11		0.0053	0.00017	240	7,400	230

[1] Based on "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (September 26, 2011); includes data from PHED/ORETF/AHETF .
[2] Based on proposed label.
[3] Exposure Science Advisory Council Policy #9.1.
[4] Dermal Dose = Dermal Unit Exposure (mg/lb ai) x Application Rate (lb ai/acre) x Area Treated (Acres/day) x DAF (6%)/BW (80 kg).
[5] Inhalation Dose = Inhalation Unit Exposure (mg/kg) x Application Rate (lb ai/acre) x Area Treated (Acres/day) x DAF (6%)/BW (80 kg).
[6] Dermal MOE = Dermal NOAEL (1.25 mg/kg/day)/Dermal Dose (mg/kg/day). Level of concern = 100.
[7] Inhalation MOE = Inhalation NOAEL (1.25 mg/kg/day)/ Inhalation Dose (mg/kg/day). Level of concern = 100.
[8] Total MOE = NOAEL (mg/kg/day)/Dermal Dose + Inhalation Dose.

Table 13. Occupational Handler Short- and Intermediate-Term Dermal and Inhalation Exposure and Risk Estimates for Potato Post-Harvest Use									
Exposure Scenario	**Solution Conc.[2] (lb ai/gal soln)**	**Amount Treated/ Day[3] (gal/lb)**	**Amount Processed[4] (lbs/hr)**	**Dermal UE (mg/lb ai)**	**Inhal. UE[5] (mg/lb ai)**	**Daily Dose[6] (mg ai/kg/day)**		**MOEs LOC=100**	
						Dermal	**Inhal.**	**Dermal**	**Inhal.**
Open Mixing/Loading Liquids	0.014	0.00025	180,000	0.220	0.000219	0.00084	0.000014	1,500	90,000

1. Liquid Formulation – Thesis EPA Reg. No. 100-1386
2. Solution Concentration - fl oz product/gal water x lb ai/gal product x 1 gal/128 fl oz (e.g. 0.3 fl oz product/0.5 gal water x 3 lb ai/gal product x 1 gal/128 fl oz)
3. Amount Treated Per day - gallons/lb of tubers (e.g. 0.5 gal treats 2,000 lb tubers = 1 gal/4,000 lb tubers). Provided by the registrant, in an email correspondence.
4. Amount Processed - lbs boxes per hour. Assumed that a packing facility could potentially pack 2,000 boxes per hour, each weighing 90 lbs (2,000 boxes/hr x 90 lbs/box = 180,000 lbs/hr)
5. Unit Exposure Values - Baseline (e.g. no gloves or respirator)
6. Short- a nd Intermediate Term Inhalation Daily Dose - [Amount Processed (lb boxes/hr) x Amount Treated daily (gal/lb) x soln concentration (lb ai/gal soln) x Unit Exposure x 8 (hr/day) x absorption factor (0.06 dermal only]/body weight
7. Short Term MOE - NOAEL (1.25 mg/kg/day)/Daily Dose (mg ai/kg/day)
8. Intermediate Term MOE - NOAEL (1.25 mg/kg/day)/Daily Dose (mg ai/kg/day)

9.2 Post-Application Exposure

HED uses the term "post-application" to describe those individuals who can be exposed to pesticides after entering areas previously treated with pesticides and performing certain tasks or activities (also often referred to as reentry exposure). Post-application exposures are expected to occur primarily via the dermal route. Post-application exposures are expected to occur primarily via the dermal route. Based on the Agency's current practices, a quantitative post application inhalation exposure assessment was not performed for difenoconazole. However, volatilization of pesticides may be a potential source of post application inhalation exposure to individuals nearby to pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009. The Agency received the

SAP's final report on March 2, 2010 and is in the process of evaluating the SAP report. The Agency may, as appropriate, develop policies and procedures to identify the need for and, subsequently, the way to incorporate post application inhalation exposure into the Agency's risk assessments. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative post application inhalation exposure assessment.

9.2.1 Post-Application Exposure Scenarios

There are no compound specific data with which to estimate post-application exposures to agricultural workers. Estimates of post-application re-entry exposure to agricultural workers are based upon the EXPOSAC Standard Operating Procedures (SOPs) (3.1, Reference 4). This SOP lists a number of possible post-application agricultural activities for the proposed crop uses that might result in post-application.

The following post-application exposure scenarios were assessed for proposed post-emergence uses of difenoconazole.

- Citrus fruits, Crop group 10-10; hand harvesting, hand pruning, scouting, hand weeding, orchard maintenance
- Fruiting Vegetable Crop group 8-10; irrigation (hand set), hand harvesting, tying/training, transplanting, scouting, hand pruning; scouting; thinning, hand weeding
- Pome Fruit Crop group 11-10; hand harvesting, thinning, training, transplanting, hand weeding, propping, orchard maintenance.
- Strawberry and other low growing berry (subgroup 13-07G, except cranberry); hand harvesting, leaf pulling, tying/training, irrigation (hand set), scouting, propagating, hand pruning, trellis repair; transplanting, hand pruning (shears); hand weeding, canopy management
- Post-harvest potato; sorting, packing and culling treated potatoes

In accordance with the Worker Protection Standard (WPS), a 12-hr restricted entry interval (REI) is required for chemicals classified under Toxicity Category III/IV.

9.2.2 Post Application Exposure Data and Assumptions for Field Crops

- Average body weight of an adult handler is 70 kg.
- Dermal absorption factor is 6%
- Exposure duration is 8 hrs per day
- Maximum label application rates:
  - 0.125 lb ai/A for citrus fruits
  - 0.11 lb ai /A for fruiting vegetables
  - 0.07 lb ai/A for pome fruit
  - 0.114 lb ai/A for low growing berries
- Transfer Coefficients:
  - 100 – 1400 cm^2/hour for citrus fruit post-application activities
  - 70 – 1900 cm^2/hour for fruiting vegetable post-application activities
  - 100 – 3600 cm^2/hour for pome fruit post-application activities
  - 70 – 5500 cm^2/hour for low growing berry post-application activities
- Initial fraction of ai retained on foliage is 20%
- Exposure is assumed to occur on the day of application (day 0)

9.2.3 Post Application Exposure Assumptions for Post-Harvest Potato

The proposed occupational uses for difenoconazole addressed in this document involve post-harvest applications, resulting in the potential for exposure during sorting, packing and culling treated potatoes. Therefore a dermal risk assessment was performed. The estimates of exposure is derived from residue chemistry data, surface area calculations, a reentry study for citrus (used as surrogate) found in the scientific literature, and a study monitoring the amount of material transferred during contact with a treated surface (Refer to ExpoSAC draft policy by D. Jaquith, 11/2005).

- A "standard" potato has a diameter of 2.25 to inches in diameter and weighs 213 grams;
- The residue level of pesticide for potatoes used in this assessment is 2.34 ppm (µg/g) obtained from chemical specific data (highest average field trial (HAFT) for this commodity.
- All of the pesticide residue is on the surface of the commodity. The chemical is not applied as a systemic product.
- Workers are assumed to perform the sorting/culling tasks for 8 hours per day.
- Dermal absorption is 6% for difenoconazole.
- The transfer efficiency of the chemical is less than 2 percent.
- The transfer coefficient for the palmar surface of the hands only is 408 cm^2 per hour.

9.2.4 Post-Application Exposure and Risk Estimates

A target LOC or MOE of 100 is considered adequate for dermal exposure. Post-application exposure and risk estimates are not of concern (MOEs > 100). A summary of post-application exposure and risk calculations, assumptions, and results is provided in Tables 14 and 15.

Table 14. Estimated Difenoconazole Exposure & MOEs for Occupational Post-Application Exposure						
Exposure Scenario	**Post-application Activities**	**TC (cm^2/hr)**	**App Rate (lb ai/A)**	**DFR (mg/cm^2)**	**Dermal Dose (mg/kg/day)**	**MOE LOC = 100**
Citrus fruits, Crop group 10-10	Harvesting, Hand	1400	0.125	0.00028	0.0024	530
	Pruning, Hand; Scouting	580	0.125	0.00028	0.0010	1300
	Transplanting	230	0.125	0.00028	0.0004	3200
	Baiting/Trapping; Weeding, Hand; Orchard maintenance	100	0.125	0.00028	0.0002	7400
Fruiting Vegetable, Crop group 8-10	Irrigation (hand set)	1900	0.11	0.00025	0.00281	440
	Harvesting, Hand; Tying/Training	1100	0.11	0.00025	0.00163	770
	Harvesting, Hand; Tying/Training	550	0.11	0.00025	0.00081	1500
	Transplanting	230	0.11	0.00025	0.00034	3700
	Scouting	210	0.11	0.00025	0.00031	4000
	Pruning, Hand; Scouting; Thinning Fruit; Weeding, Hand	90	0.11	0.00025	0.0001	9400
	Weeding, Hand; Pruning, Hand	70	0.11	0.00025	0.0001	12000
Pome Fruit, Crop Group 11-10	Thinning Fruit	3600	0.07	0.00016	0.0034	370
	Harvesting, Hand	1400	0.07	0.00016	0.0013	950
	Scouting; Pruning, Hand; Training	580	0.07	0.00016	0.00055	2300
	Transplanting	230	0.07	0.00016	0.00022	5800
	Weeding, Hand; Propping; Orchard maintenance	100	0.07	0.00016	0.00009	13000
Strawberry and other low growing berry (subgroup 13-07G, except cranberry)	Harvesting, Hand; Leaf Pulling; Tying/Training	5500	0.114	0.00026	0.0084	150
	Irrigation (hand set)	1900	0.114	0.00026	0.0029	430
	Harvesting, Hand; Tying/Training;	1400	0.114	0.00026	0.0021	580
	Harvesting, Hand; Harvesting; Scouting;	1100	0.114	0.00026	0.0017	740
	Propagating; Pruning, Hand; Scouting; Trellis Repair; Tying/Training; Weeding, Hand	640	0.114	0.00026	0.0010	1300
	Transplanting	230	0.114	0.00026	0.00035	3500
	Scouting	210	0.114	0.00026	0.00032	3900
	Pruning, Hand (shears); Weeding, Hand; Canopy Management	70	0.114	0.00026	0.00011	12000

1. DFR = AR x F x $(1\text{-}D)^t$ x 4.54E8 µg/lb x 2.47E-8 $acre/cm^2$
2. MOE = POD (NOAEL, 1.25 mg/kg/day) / Daily Dermal Dose. Daily Dermal Dose = [DFR ($\mu g/cm^2$) x TC x 0.001 mg/µg x 8 hrs/day x 6% dermal absorption] ÷ body weight 80 kg adult).

Table 15. Summary of Estimated Post Harvest Post-application MOEs for Potatoes						
Chemical in Specific Commodity[1] (Potato)			Commodity Specific Surface area (cm^2)	Surface Residue ($\mu g/cm^2$)	Daily Dose[2] (mg /kg /day)	Short & Int-Term MOE[3] LOC = 100
Chemical Residue µg /g (PPM)	Commodity Avg. Weight (g)	Chemical Residue (µg)/ Commodity				
2.34	213	498	214	2.3	0.000114	11,000

[1]Residue level calculations for potatoes based on highest average field trial

[2]Daily Dose = [(408 cm^2/hr) x (2.3µg/cm^2) x (8 hrs/day) x (6% of Dermal Absorption) x (2% Transfer Efficiency) x (0.001 mg/µg)]/80 Kg

[3] MOEmat = NOAEL / Daily Dose. (Short & Intermediate-Term NOAEL = 1.25 mg/kg/day)

10.0 REFERENCES

Difenoconazole. Petition for Postharvest (PH) Use on Potatoes and Expansions of Existing Crop Group/Representative Commodity Uses to Fruiting Vegetables Group 8-10, Citrus Fruits Group 10-10, Pome Fruits Group 11-10, and Low growing Berry Subgroup 13-07G, Except Cranberry. Summary of Analytical Chemistry and Residue Data, B. Cropp-Kohlligian, D389912, 5/30/12

Difenoconazole. Acute and Chronic Aggregate Dietary Exposure and Risk Assessments for the Petition for Postharvest (PH) Use on Potatoes and Expansions of Existing Crop Group/Representative Commodity Uses to Fruiting Vegetables Group 8-10, Citrus Fruits Group 10-10, Pome Fruits Group 11-10, and Low growing Berry Subgroup 13-07G, Except Cranberry. T. Morton, D397664, 5/30/12

Difenoconazole. Occupational and Residential Exposure Assessment to Evaluate the Risk from Proposed Uses on Post-Harvest Potatoes, and the Expansion of Various Crop Groups Including: Citrus Fruit Group 10-10; Fruiting Vegetable Subgroups 8-10; Low Growing Berry Subgroup 13-07G, except cranberry; Pome Fruit, Crop Group 11-10 and Fruiting Vegetable, Crop Group 8-10), Ivan Nieves, D398608, 5/30/12

Difenoconazole (Parent Only) Drinking Water Assessment in Support of New Use Registration Action for Golf Course Turf. I. Maher, D371044, 6/1/10, Updated EFED; Memo, F. Khan, 23-February-2012; D398836

Difenoconazole. Request for Restatement of 1994 EPA Cancer Classification and Risk Assessment Approach Using Current Terminology. P.V. Shah, D 318039, 3/1/07

Difenoconazole – with both available in vivo and in vitro dermal absorption studies, select an appropriate dermal absorption factor to be used for risk assessment, J. Chen, 12/18/08

Difenconazole: Summary of Hazard and Science Policy Council (HASPOC) Meeting of February 23, 2012: Recommendations on the need for a 28-day inhalation study, D. Smegal, TXR#0054074, 3/5/12.

APPENDICES

A. TOXICOLOGY DATA SUMMARY

A.1 Guideline Data Requirements

Guideline No.	Study Type	Technical		MRID No.
		Required	Submitted	
870.3100	Subchronic (Oral) Toxicity - Rodent.....	Y	Y	42090022 42090021
870.3150	Subchronic (Oral) Toxicity - Non-Rodent	Y	Y	42090013
870.3200	21/28-Day Dermal Toxicity	N	Y	42090013 46950310
870.3250	90-Day Dermal Toxicity	N	N	
870.3465	90-Day Inhalation Toxicity	N	N	
870.3700a	Prenatal Developmental Toxicity - Rodent	Y	Y	42090016 42710008
870.3700b	Prenatal Developmental Toxicity - Non-Rodent.	Y	Y	42090017 42710008
870.3800	Reproduction and Fertility Effects	Y	Y	42090018
870.4100a	Chronic (Oral) Toxicity - Rodent.....	Y	Y	42090015 42710006
870.4100b	Chronic (Oral) Toxicity - Non-Rodent (Dog)	Y	Y	42090012 42710005
870.4200a	Carcinogenicity - Rat…….....	Y	Y	42090019 42710010
870.4200b	Carcinogenicity - Mouse	Y	Y	42090015 42710006
870.4300	Combined Chronic Toxicity /Carcinogenicity	Y	Y	42090015 42710006
870.6100a	Neurotoxicity - Acute Delayed Neurotox.- Hen..	N	N	---
870.6100b	Neurotoxicity - Subchronic - Hen	N	N	---
870.6200a	Neurotoxicity - Acute - Rat	Y	Y	46950327
870.6200b	Neurotoxicity -Subchronic - Rat	Y	Y	46950329
870.6300	Developmental Neurotoxicity……	N	N	--
870.7800	Immunotoxicity……..	Y	Y	--

A.2 Toxicity Profiles

Table A.1. Acute Toxicity Profile – Difenoconazole				
Guideline No.	**Study Type**	**MRID No.**	**Results**	**Toxicity Category**
870.1100	Acute oral	42090006	LD_{50} = 1450 mg/kg	III
870.1200	Acute dermal	42090007	LD_{50} > 2010 mg/kg	III
870.1300	Acute inhalation	42090008	LC_{50} > 3.3 mg/L	III
870.2400	Eye irritation	42090009	Mild irritation reversible in 7 days	III
870.2500	Dermal irritation	40789807	Slight irritation	IV
870.2600	Skin sensitization	42090011, 42710004	Negative	N/A

Table A.2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	90-Day oral toxicity (rat)	42090022 (1987) Acceptable/guideline 0, 20, 200, 750, 1500 or 3000 ppm 0, 1, 10, 37.5, 75 and 150 mg/kg/d	NOAEL = 20 ppm (1 mg/kg/day) LOAEL = 200 ppm (10 mg/kg/day) based on the 10% decrease in body weight in the 200 ppm females (as well as a negative trend in feed consumption) and Increases in absolute liver weights in both sexes
870.3100	90-Day oral toxicity (mouse)	42090021 (1987) Minimum/guideline 0, 20, 200, 2500, 7500 or 15,000 ppm M: 0, 2.9, 30.8, 383.6, 1125 and 2250 mg/kg/d F: 0, 4.1, 41.5, 558.9, 1125 and 2250 mg/kg/d	NOAEL = 20 ppm (2.9 mg/kg/day) LOAEL = 200 ppm (30.8 mg/kg/day) based on body weight changes & liver histopathology.
870.3150	26-Week oral toxicity	42090012 (1987) Minimum/ guideline 0, 100, 1000, 3000 or 6000 ppm M: 0, 3.6, 31.3, 96.6 and 157.8 mg/kg/d F: 0, 3.4, 34.8, 110.6 and 203.7 mg/kg/d	NOAEL = 3000 ppm (31.3 mg/kg/day in males/34.8 mg/kg/day in females) LOAEL = 6000 ppm (96.6 mg/kg/day in males/110.6 mg/kg/day in females), based primarily on microscopic examination of CGA 169374-related lenticular cataracts.
870.3200	21/28-Day dermal toxicity (rat)	42090013 (1987) Minimum/ guideline 0, 10, 100 and 1000 mg/kg/d	NOAEL = 10 mg/kg/day LOAEL = 100 mg/kg/day based on statistically significant decrements in body weight, body weight gain, and food consumption.
870.3200	21/28-Day dermal toxicity (rat)	46950310 (2000) Acceptable/ guideline 0, 10, 100 and 1000 mg/kg/d	NOAEL (systemic) = 1000 mg/kg/day LOAEL (systemic) was not determined. NOAEL (dermal) = 100 mg/kg/day LOAEL (dermal) = 1000 mg/kg/day based on hyperkeratosis at the skin application site.
870.3700a	Prenatal developmental in (rat)	42090016, 42710007 (1987) Minimum/ guideline 0, 2, 20, 100 or 200 mg/kg/d from GD 6-15 (nominal doses differed widely from theoretical, this required altering NOAEL/LOAEL values)	Maternal NOAEL = 16 mg/kg/day LOAEL = 85 mg/kg/day based on decreased body weight gain and food consumption. Developmental NOAEL = 85 mg/kg/day LOAEL = 171 mg/kg/day based on alterations in fetal ossification.

Table A.2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700b	Prenatal developmental in (rabbit)	42090017, 42710008 (1987) Minimum/ guideline 0, 1, 25 or 75 mg/kg/d from GD 7-19	Maternal NOAEL = 25 mg/kg/day LOAEL = 75 mg/kg/day based on decreased body weight gain and food consumption. Developmental NOAEL = 25 mg/kg/day LOAEL = 75 mg/kg/day based on nonsignificant increases in postimplantation loss and resorptions/doe and a significant decrease in fetal weight.
870.3800	Reproduction and fertility effects (rat)	42090018 (1988) Minimum/ guideline 0, 25, 250 or 2500 ppm 0, 1.25, 12.5 and 125 mg/kg/d	Parental/Systemic NOAEL = 25 ppm (1.25 mg/kg/day) LOAEL = 250 ppm (12.5 mg/kg/day) based on reductions (statistically nonsignificant) in body weight gain which appear to be part of a dose-related trend days 70-77 prior to mating, days 0-7 of gestation, and days 7-14 of lactation Offspring NOAEL = 25 ppm (1.25 mg/kg/day) LOAEL = 250 ppm (12.5 mg/kg/day) based on a significant reduction in the body weight of F1 male pups at day 21 in the 250 ppm group.
870.4100b	Chronic toxicity (dog)	42090012, 42710005 (1988) Minimum/ guideline 0, 20, 100, 500 or 1500 ppm M: 0, 0.71, 3.4, 16.4 and 51.2 mg/kg/d F: 0, 0.63, 3.7, 19.4 and 44.3 mg/kg/d	NOAEL = 100 ppm (3.4 mg/kg/day in males/3.7 mg/kg/day in females) LOAEL = 500 ppm (16.4 mg/kg/day in males/19.4 mg/kg/day in females), based on significant inhibition of body weight gain in females.
870.4200	Carcinogenicity (rat)	42090019, 42710010 (1989) Minimum/ guideline 0, 10, 20, 500 or 2500 ppm M: o, 0.48, 0.96, 24.12 and 123.7 mg/kg/d F: 0, 0.64, 1.27, 32.79 and 169.6 mg/kg/d	NOAEL = 20 ppm (0.96 mg/kg/day in males/1.27 mg/kg/day in females) LOAEL = 500 ppm (24.1 mg/kg/day in males/ 32.8 mg/kg/day in females) based on reductions in cumulative body weight gains in the 500 and 2500 ppm groups. No evidence of carcinogenicity
870.4300	Carcinogenicity (mouse)	42090015, 42710006 (1989) Minimum/ guideline 0, 10, 30, 300, 2500 or 3000 ppm M: 0, 1.51, 4.65, 46.29, 423.1 and 818.9 mg/kg/d F: 0, 1.9, 5.63, 57.79 and 512.6 mg/kg/d	NOAEL = 30 ppm (4.7 mg/kg/day in males/5.6 mg/kg/day in females) LOAEL = 300 ppm (46.3 mg/kg/day in males/57.8 mg/kg/day in females) based on reductions in the cumulative body weight gains and hepatocellular hypertrophy, liver necrosis, fatty changes in the liver and bile stasis in the 300, 2500 & 4500 ppm groups. Evidence of carcinogenicity (liver adenoma/carcinoma in both sexes)
870.5100	*In vitro* bacterial gene mutation *(Salmonella typhimurium/ E. coli)*/ mammalian activation gene mutation assay	42090019, 42710010 (1989) Minimum/ guideline 340 - 5447 µg/plate; 85 - 1362 µg/plate (repeat assay with TA1537 and TA98)	There were sufficient and valid data to conclude that CGA 169374 technical was negative in the microbial gene mutation assay.

Table A.2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.5300	*in vitro* mammalian cell gene mutation assay in mouse lymphoma cells	42090024 (1986) Unacceptable/ guideline	No conclusion can be reached from the three nonactivated and two S9 activated mouse lymphoma forward mutation assays conducted with difenoconazole technical. The study was seriously compromised.
870.5375	*In vitro* Mammalian Cytogenetics (chromosomal aberrations) assay in Chinese hamster CHO cells	46950319 (2001) Acceptable/ guideline 0, 21.99, 27.49, or 34.36 µg/mL (-S9) 0, 34.36, 53.69 or 67.11 µg/mL (+S9)	There was evidence of a weak induction of structural chromosomal aberrations over background in the presence of S9-mix.
870.5375	*In vitro* Mammalian Cytogenetics (chromosomal aberrations) assay in Chinese hamster CHO cells	46950321 (2001) Acceptable/ guideline 0, 26.3, 39.5 or 59.3 µg/mL (-S9) 0, 11.7 or 17.6 µg/mL (+S9)	There was evidence of a weak induction of structural chromosomal aberrations over background.
870.5375	*In vitro* Mammalian Cytogenetics (chromosomal aberrations) assay in human lymphocytes	46950323 (2001) Acceptable/ guideline 0, 5, 30 or 75 µg/mL (-S9) 0, 5, 30 or 62 µg/mL (+S9)	There was no evidence of structural chromosomal aberrations induced over background.
870.5385	*In vivo* mammalian chromosomal aberration test Assay in Mice	42090023 (1986) Unacceptable/guideline 250, 500 or 1000 mg/kg	There was no evidence of a cytotoxic effect on the target organ or significant increase in the frequency of nuclear anomalies (micronuclei). However, the study was compromised.
870.5395	*In vivo* mammalian cytogenetics - erythrocyte micronucleus assay in mice	41710011 (1992) Acceptable/guideline Doses up to 1600 mg/kg	Mice bone marrow - No increase in micronucleated polychromatic erythrocytes occurred with CGA-1 69374 (91.2% a.i).
870.5550	Unscheduled DNA Synthesis in Mammalian Cells in Culture	4210012 (1992) Acceptable/ guideline Doses up to 50 µg/mL	CGA-i69374 tech. (92.2% a.i.) was considered to be negative in the unscheduled DNA synthesis assay in rat primary hepatocytes as measured by an autoradiographic method at concentrations up to 50.0 µg/mL.
870.5550	Unscheduled DNA Synthesis in Mammalian Cells in Culture	42090027 (1985) Unacceptable/ guideline 0.25-31.25 µg/mL	No conclusion can be reached from the unscheduled DNA synthesis (UDS) primary rat hepatocyte assay conducted with difenoconazole technical at concentrations ranging from 0.25 to 31.25 µg /mL. The sensitivity of the study was severely compromised.

Table A.2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.5550	Unscheduled DNA Synthesis in Mammalian Cells in Culture	42090026 (1985) Unacceptable/ guideline 0.08-10 µg/mL	No conclusion can be reached from the unscheduled DNA synthesis (UDS) human fibroblast assay conducted with difenoconazole tech. at conc. ranging from 0.08 to 10 µg /mL.
870.6200a	Acute neurotoxicity screening battery	46950327 (2006) Acceptable/ guideline 0, 25, 200 or 2000 mg/kg/d	NOAEL (M) = 25 mg/kg/day LOAEL (M) = 200 mg/kg/day based on reduced fore-limb grip strength in males on day 1 and increased motor activity on Day 1. NOAEL (F) = 200 mg/kg/day LOAEL (F) = 2000 mg/kg/day based on decreased body weight, the following clinical signs: upward curvature of the spine, tip-toe gait, decreased activity, piloerection and sides pinched in and decreased motor activity.
870.6200b	Subchronic neurotoxicity screening battery	46950329 (2006) Acceptable/ guideline 0, 40, 250, or 1500 ppm M; 0, 2.8, 17.3 or 107.0 mg/kg/d F: 0, 3.2, 19.5, or 120.2 mg/kg/d	NOAEL (M) = 40 ppm (2.8 mg/kg/day) LOAEL (M) = 250 ppm (17.3 mg/kg/day) based on decreased hind limb strength. NOAEL (F) = 250 ppm (19.5 mg/kg/day) LOAEL (F) = 1500 (120.2 mg/kg/day) based on decreased body weight, body weight gain and food efficiency.
870.7485	Metabolism and pharmacokinetics (rat)	42090028 (1990) Acceptable/ guideline 14 daily doses of 0.5 or 300 mg/kg	Male and female Sprague-Dawley rats. Animals were administered a single oral gavage dose of 0.5 or 300 mg/kg [^{14}C]CGA- 169374, or 0.5 mg/kg unlabeled GGA-169374 by gavage for 14 days followed by a single gavage dose of 0.5 mg/kg [^{14}C)CGA-169374 on day 15. The test compound was labeled with C^{14} at either the phenyl or triazole ring.
870.7485	Metabolism and pharmacokinetics (rat)	42090028 (1990) 42090029 (1987) 42090030 (1987) 42090031 (1988) Acceptable/ guideline Single oral dose 0.5 or 300 mg/kg 14 daily doses of 0.5 or 300 mg/kg	Male and female Sprague-Dawley rats. Animals were administered a single oral gavage dose of 0.5 or 300 mg/kg [^{14}C]CGA- 169374, or 0.5 mg/kg unlabeled GGA-169374 by gavage for 14 days followed by a single gavage dose of 0.5 mg/kg [^{14}C)CGA-169374 on day 15. The test compound was labeled with C^{14} at either the phenyl or triazole ring. [^{14}C] CCA 169374 was rapidly and extensively distributed, metabolized, and excreted in rats for all dosing regimens. The metabolism of difenoconazole appears to be extensive because the metabolites accounted for most of the recovered radioactivity in the excrete. Three major metabolites were identified in the feces (i.e. metabolites A, B, and C). Two of the metabolites were separated into isomers (i.e., Al, A2, B1, and B2). Metabolite C was detected only in the high-dose groups, indicating that metabolism of difenoconazole is dose-related and involves saturation of the metabolic pathway. Free triazole metabolite was detected in the urine of triazole-labeled groups and its byproduct was detected in the liver of phenyl labeled groups only. Other urinary metabolites were not characterized.

Table A.2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.7485	Metabolism and pharmacokinetics (rat)	42090028 (1990) 42090029 (1987) 42090030 (1987) 42090031 (1988) Acceptable/ guideline in conjunction with MRIDs 420710013, 42710014 listed below Single oral dose 0.5 or 300 mg/kg 14 daily doses of 0.5 or 300 mg/kg	The absorption, distribution, metabolism, and excretion of CGA 169374 were studied in groups of male and female Sprague-Dawley rats. Animals were administered a single oral gavage dose of 0.5 or 300 mg/kg [^{14}C]CGA-169374, or 0.5 mg/kg unlabeled GGA-169374 by gavage for 14 days followed by a single gavage dose of 0.5 mg/kg [^{14}C)CGA-169374 on day 15. The test compound was labeled with C^{14} at either the phenyl or triazole ring. **[^{14}C] CCA 169374 was rapidly and extensively distributed, metabolized, and excreted in rats for all** dosing regimens. the extent of absorption is undetermined pending determination of the extent of biliary excretion. The 4-day recoveries were 97.94-107.75% of the administered dose for all dosing groups. The elimination of radioactivity in the feces (78.06-94.61% of administered dose) and urine (8.48-21.86%) were almost comparable for all oral dose groups, with slightly higher radioactivity found in the feces of the high-dose group than the low-dose groups. This was probably due to biliary excretion, poor absorption or saturation of the metabolic pathway. The radioactivity in the blood peaked at about 24-48 hours for an dosing group. Half-lives of elimination appear to be approximately 20 hours for the low-dose groups and 33-48 hours for the high-dose group. The study results also indicate that difenoconazole and/or its metabolites do not bioaccumulate to an appreciable extent following oral exposure since all the tissues contained negligible levels (< 1%) of radioactivity 7 days postexposure. The metabolism of difenoconazole appears to be extensive because the metabolites accounted for most of the recovered radioactivity in the excrete. Three major metabolites were identified in the feces (i.e. metabolites A, B, and C). Two of the metabolites were separated into isomers (i.e., Al, A2, B1, and B2). Metabolite C was detected only in the high-dose groups, indicating that metabolism of difenoconazole is dose-related and involves saturation of the metabolic pathway. Free triazole metabolite was detected in the urine of triazole-labeled groups and its byproduct was detected in the liver of phenyl labeled groups only. Other urinary metabolites were not characterized. These studies indicate that distribution, metabolism, and elimination of CGA-169374 were not sex related. There was a slight dose difference in the metabolism and elimination of CGA-169374. In phenyl and triazole labeling studies, fecal excretion of radioactivity was higher in the high dose animals compared to the low dose animals, and an additional metabolite was found in the feces of the high dose animals compared to the low dose animals. There was no major difference in the distribution and excretion of radioactivity with labeling at the phenyl and triazole ring positions, however, there were some different metabolites identified. The studies also showed that administration of 0.5 and 300 mg/kg CGA- 169314 did not induce any treatment related clinical effects.

APPENDIX A.3 HAZARD IDENTIFICATION AND ENDPOINT SELECTION

A.3.1 Acute Population Adjusted Doses (aPAD) – All Populations

Selected Study: Acute Neurotoxicity Study in Rats
MRID 46950327
Dose and Endpoint for Establishing an aPAD: NOAEL is 25 mg/kg/day. LOAEL is 200 mg/kg/day based on reduced fore-limb grip strength in males on day 1.
Uncertainty Factor (UF): 100 This includes 10x for interspecies extrapolation and 10x for intraspecies variation.
Comments about Study/Endpoint: The selected endpoint is considered appropriate for acute dietary exposure because effects were seen after a single dose. The endpoint is protective of the general population and all subpopulations for effects seen in the acute neurotoxicity study in rats. It is also protective of developmental and maternal effects observed in the rabbit developmental toxicity study at the LOAEL of 75 mg/kg/day and NOAEL of 25 mg/kg/day.

$$\textbf{General Population aPAD} = \frac{\text{(NOAEL) 25 mg/kg}}{\text{(UF) 100}} = \textbf{0.25 mg/kg}$$

A.3.2 Chronic Population Adjusted Dose (cPAD) – All Populations

Selected Study: Chronic/Oncogenicity Study in Rats
MRID 42090019/20
Dose and Endpoint for Establishing an cPAD: The NOAEL is 0.96 mg/kg/day. The LOAEL is 24.12 mg/kg/day based on cumulative decreases in body weight gains at 24.12 mg/kg/day in males.
Uncertainty Factor (UF): 100 This includes 10X for interspecies extrapolation and 10x for intraspecies variation.

$$\textbf{General Population cPAD} = \frac{\text{(NOAEL) 0.96 mg/kg/day}}{\text{(UF) 100}} = \textbf{0.01 mg/kg/day}$$

A.3.3 Incidental Oral Exposure (Short-Term)

Selected Study: Two Generation Reproduction Study in Rats
MRID 42090018
Dose and Endpoint for Establishing POD: The NOAEL is 1.25 mg/kg/day based on decreased pup weight in males at 12.5 mg/kg/day (LOAEL) on day 21, and reductions in body weight gain in F0 females.
Uncertainty Factor (UF): An MOE 100 is required for the short- and intermediate-term scenarios for dermal exposure is based on the conventional uncertainty factor of 100. This includes 10x for interspecies extrapolation and 10x for intraspecies variation.

Comments about Study/Endpoint: There are no residential uses for difenoconazole that would

result in incidental oral exposure to children. However, a short term oral exposure endpoint is required for aggregate risk assessment.

A.3.4 Dermal Absorption

A dermal absorption factor (DAF) is applied when dermal exposure endpoints are selected from oral toxicity studies. The dermal factor converts the oral dose to an equivalent dermal dose for the risk assessment. A DAF of 6% was selected for use in risk assessment based on available in vivo dermal absorption studies in rat and in vitro dermal absorption studies conducted with rat and human skin. The DAF was selected by a special working group of the Antimicrobials Division Toxicity Endpoint Selection Committee (12/18/08 memorandum from J. Chen to M. Swindell – Attachment A.3).

A.3.5 Dermal Exposure (Short and Intermediate-Term)

Selected Study: Two Generation Reproduction Study in Rats (MRID 42090018)

See Section A.4.3

Dose and Endpoint for Establishing POD: The NOAEL is 1.25 mg/kg/day based on decreased pup weight in males at 12.5 mg/kg/day (LOAEL) on day 21 and reductions in body weight gain in F0 females.. Dermal absorption is 6%.

Uncertainty Factor (UF): An MOE 100 is required for the short- and intermediate-term scenarios for dermal exposure is based on the conventional uncertainty factor of 100. This includes 10x for interspecies extrapolation and 10x for intraspecies variation.

Comments about Study/Endpoint: Although dermal toxicity studies are available, a POD from an oral study was selected because effects in young animals (decreased pup weight) the primary effect of concern for short, intermediate and long term exposure is not specifically evaluated in the available dermal toxicity studies that only assess adult animals. The selected endpoint is protective of offspring effects from dermal exposure. A DAF of 6% is applied to the POD for dermal exposure.

A.3.6 Inhalation Exposure (Short- and Intermediate-Term)

Selected Study: Two Generation Reproduction Study in Rats (MRID 42090018)

See Section A.4.3

A.4 EXECUTIVE SUMMARIES FOR SUPPORTING TOXICITY STUDIES

A.4.1 Subchronic Toxicity

870.3100 90-Day Oral Toxicity – Rat MRID 42090022

CGA-169374 Technical was administered orally in feed admixtures to six groups of rats of both sexes at 0 ppm, 20 ppm, 200 ppm, 750 ppm, 1500 ppm, and 3000 ppm for 13 weeks. The results of this dietary subchronic evaluation of the toxicity of the test article were generally unremarkable. There was a significant trend for decreased body weights in both sexes, and the 200 ppm female rats showed an approximate 10% decrease in body weight relative to their controls concomitant with decreased food consumption. There was one dose—related effect of the chemical discovered during the histopathology examination, that identified modest diffuse hepatocellular enlargement, vis a vis. increased liver weights, in rats of both sexes at the two highest doses tested. Additionally, although not statistically significant, compared to the other groups there was an increase in the frequency and quantity of ketones in the urine of group 6 males. The presence of elevated ketone levels may be due to gluconeogenesis driven by decreased protein intake from the diet as a result of decreased food intake. The somewhat compromised nutritional status of the rats could possibly and indirectly have promoted the hepatocellular enlargement as well.
It is possible to conclude from this study, that based on approximately 10% decrease in body weight in the 200 ppm females (concomitant with a negative trend for food consumption) and increases in absolute liver weights in both sexes appearing at 750 ppm, the LOAEL is 200 ppm. The NOAEL was 20 ppm.
Core Classification: Minimum

870.3100 90-Day Oral Toxicity – Mouse MRID 42090021

CGA 169374 was offered in feed admixtures to five groups of mice composed of 15 animals/group/sex and 20 mice per sex for controls in dietary concentrations of 20 ppm, 200 ppm, 2500 ppm, 7500 ppm, or 15000 ppm for 13 weeks. Most of the mice fed 7500 ppm or 15,000 ppm test article, groups 5 and 6 respectively, died during the first week on study. There were some CGA 169374-related effects. The statistical analysis of total food consumption and body weight changes over the course of the study showed significantly reduced body weight gain for paired group 4 (2500 ppm) females and a significant negative trend. Compound—related effects from histologic examination were confined to the liver. Hepatotoxicity in mice that DOS was evidenced by hepatocellular enlargement and necrosis of individual hepatocytes. Those mice that survived to the end of the study showed hepatotoxicity that included hepatocellular enlargement in group 4 animals and group 3 males and hepatocytic vacuolization in group 4 animals. Furthermore, coagulative necrosis was observed in the livers of 4/9 group 4 females. This finding, however, was not considered treatment related, because the foci were frequently small and random. The animals in groups 5 and 6, which represent the unscheduled deaths, had a high incidence of changes consistent with stress. The changes included lymphoid depletion or necrosis of the spleen, lymph nodes, and thymus, hypocellularity of the femoral marrow, mucosal erosion/ulceration of the glandular stomach, and in the female mice necrosis of individual cells in the adrenal cortex, specifically in the zona reticularis. Hyperkeratosis of the

nonglandular stomach was observed in males especially from group 6. The study director suggests the "stress" effects may be related to inappetence and a failure to eat as opposed to a direct effect of the test article. On the strength of the available data as they relate to the dose levels tested and to the parameters observed, the body weight changes and the liver histopathology form the basis for setting the NOAEL at 20 ppm, and the LOAEL at 200 ppm. The mortality data indicate the MTD was exceeded and is likely S 7500 ppm.

870.3150 26 Week Oral Feeding study –dog OPPTS MRID 42090012

CGA 169374 was offered in feed admixtures to five groups of beagle dogs composed of three animals/group/sex in dietary concentrations of 0 ppm, 100 ppm, 1000 ppm, 3000 ppm, or 6000 ppm for a minimum of 28 weeks. None of the dogs DOS. Compound— related effects, developed essentially at the 3000 ppm and 6000 ppm dose levels. The singularly most striking compound effect was bilateral lenticular cataracts ophthalmoscopically-observed in all dogs at 6000 ppm and in one female beagle at 3000 ppm. Additionally, iridic changes (irregular pupillary margins, miosis), secondary to lens induced uveitis, were also present in the affected animals. There were also reductions in mean body weight in females and males at 6000 ppm test compound throughout the study; weight loss was observed during the first three weeks on study. Body weight loss was precipitated by moderate to severe reductions in mean food consumption in females and males at 6000 ppm during the study with slight reductions observed in males at 3000 ppm and 1000 ppm and in one female at 3000 ppm. Furthermore, there were slight reductions in values for red blood cell count, hemoglobin, and hematocrit in females and males at 6000 ppm. There were also decrements in some serum clinical chemistry measurements including calcium and total protein in females at 6000 ppm and moderate increases in serum alkaline phosphatase in one or both sexes at 3000 ppm. There were modest alterations in several absolute and/or relative organ weight measurements to include the heart, prostate gland, salivary gland, uterus, kidney, liver, and brain at the highest dose tested (HOT). Nevertheless, liver weight measurements were also increased in Group 4 females. There were no other test article—related changes in any other parameter examined. On the strength of the available data as they relate to the dose levels tested and the parameters observed, the LOAEL and the NOAEL for the test article in female and male beagle dogs were 3000 ppm and 1000 ppm, respectively, based primarily on microscopic examination of CGA 169374-related lenticular cataracts. Core Classification: Minimum

A.4.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study – Rat MRID 42090016

CGA 169347 technical was administered by gavage on days 6-15 of gestation to presumed pregnant rats at 0, 2, 20, 100, or 20a mg/kg. Significant decreases in maternal body weight gain and feed consumption were observed during the dosing period for the feed consumption were observed during the dosing period for the 100 and 200 mg/kg groups. These animals also exhibited a significant increase in the incidence of excess salivation. There was a non significant decrease in the mean number of fetuses per dam, and non significant increases in the mean number of resorptions per dam and % postimplantation loss in the 200 mg/kg group. There was a slight (non significant) decrease in mean fetal body weight at the 200 mg/kg group. The

following represents the significant alterations in the development of fetuses in the 200 mg/kg group. The incidence of bifid or unilateral ossification of the thoracic vertebrae was significantly increased on the fetal basis. There were also significant increases in the average number of ossified hyoid and decreases in the average number of sternal centers of ossification (per fetus per litter). The average number of ribs was significantly increased (with accompanying increases in the number of thoracic vertebrae), and decreases in the number of lumbar vertebrae in this group. These findings may be related to maternal toxicity. This study may be upgraded after satisfactory review of the response to the noted deficiencies.
core classification: supplementary. NOTE: Due to the relatively high percent deviation of the actual doses tested from the theoretical concentration the effect levels have been modified accordingly. This modification may be subject to change as the purity is currently unknown.
Maternal NOAEL = 16 mg/kg; Maternal LOEL = 85 mg/kg; Developmental Toxicity NOAEL = 85 mg/kg; Developmental Toxicity LOAEL = 171 mg/kg

870.3700b Prenatal Developmental Toxicity Study – Rabbit MRID 42090017

CGA 169347 technical was administered by gavage on days 7—19 ofgestation to presumed pregnant rabbits at 0, 1, 25, or 73 mg/kg. Maternal toxicity was observed in this study as the death of one doe and abortions observed in two other high dose does. In addition, significant reductions in body weight gain of high dose does, were present days 7-10, 10—14, 7-20, and 0—29. These reductions correspond with reduced feed consumption during these intervals (significant reductions in feed consumption in the HDT were only observed during the treatment period, not after treatment). Slight nonsignificant increases in postimplantation loss and resorptions/doe were observed in the HDT. The significant decrease in fetal weight at the HDT may have been due to treatment. The significant differences in fetal weight observed at the low and mid dose were apparently not due to treatment.
Core Classification: supplementary
Maternal NOAEL = 25 mg/kg; Maternal LOEL = 75 mg/kg
Developmental Toxicity NOAEL 25 mg/kg; Developmental Toxicity LOEL = 75 mg/kg

A.4.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects – Rat MRID 42090018

In a two generation reproduction study, difenoconazole was administered in the diet to male and female rats at 0, 25, 250, or 2500 ppm [0, 1.25, 12.5, or 125 mg/kg/day, respectively]. Statistically significant reductions in body weight gains of F0 and F1 males were observed at 2500 ppm during Days 70-77 and during the course of the study [terminal body weight minus Day 0 body weight]. Significant reductions in body weight gains of F0 and F1 females were seen during the pre-mating, gestation, and lactation periods. A dose-related, but non-statistically significant decreases in body weight gain was seen in F0 females at 250 ppm during Days 70-77 prior to mating, Days 0-7 of gestation, and Days 7-14 of lactation:
At 2500 ppm, significant reductions in pup body weight were detected on Days 0, 4 [pre- and post culling], 7, 14, and 21 for males and females of both generations. There was a significant reduction in the body weight of F1 male pups on Day 21 in the 250 ppm group. The percentage of male pups in the F1 generation surviving Days 0-4 was significantly reduced in the 2500 ppm

group: For parental toxicity, the LOAEL of 250 ppm [12.5 mg/kg/day is based on the decreased maternal body weight gain; the NOAEL is 25 ppm [1.25 mg/kg/day. For offspring toxicity, the LOAEL of 250 ppm [12.5 mg/kg/day] is based on decreased pup weights at Day 21; the NOAEL is 25 ppm [1.25 mg/kg/day].

A.4.4 Chronic Toxicity

870.4100a (870.4300) Combined Chronic Toxicity/Carcinogenicity – Rat MRIDs 42090019/ -20

CGA 169374 was administered in the diet to male and female rats [80/sex/dose] for 104 weeks at 0; 10; 20; 500; and 2500 ppm. There were reductions in cumulative body weight gains in the 500 and the 2500 ppm groups. Mean liver weight was increased at week 53 and t termination in the 2500 ppm group. Hepatocellular hypertrophy was observed in the 500 and the 2500 ppm animals at termination. Additional findings in the clinical chemistry data also indicated that liver was the primary target organ for toxicity. No treatment related increased incidences of neoplastic findings were observed in this study. The NOAEL for the study was 20 ppm which was equal to 0.96 and 127 mg/kg/d for males and females respectively. The LOAEL was 500 ppm equal to 24.12 and 32.79mg/kg/day for males and females respectively based on cumulative decreases in body weight gains. Discussion of Tumor Data No treatment related increased incidences of neoplastic findings were observed in this study. Adequacy of the Dose Levels Tested The dose levels tested were considered adequate by the Cancer Peer Review Committee. (memorandum of July 27,1994 from B. Rinde of the Health Effects Division)

870.4100b Chronic Toxicity - Dog MRID 42090012

CGA 169347 was administered in the diet to male and female dogs at 0, 20, 100, 500, or 1500 ppm. The NOAEL was 100 ppm and the LOAEL was
500 ppm based on the following. Females receiving 1500 ppm in the diet had a significant reduction in body weight gain on day 7. Females in the 500 and 1500 ppm groups, although not statistically significant, had inhibited body weight gain throughout the study. These animals also had significant reductions in food consumption on days 7, 35, 70, and 357. The reduction in mean percent reticulocytes at the highest dose tested on day 359 may have been related to treatment, Significant increases (treatment related at day 85; dose—related at days 175 and 359) were observed in alkaline phosphatase in males receiving 1500 ppm. This study may be upgraded upon satisfactory review of the registrants response to the deficiencies (submission of the purity and raw daily observation data).
Classification: core—supplementary

A.4.5 Carcinogenicity

870.4200a Carcinogenicity/Chronic Study – Mice MRIDs 42090015 and 42710006

CD-I mice were fed diets containing difenoconazole at 0; 10; 30; 300; 2500or 4500 [males only] for 78 weeks. The NOAEL was 30 ppm equal to 4.65 mg/kg/d in males and 5.63mg/kg/d in

females respectively. The LOAEL was 300 ppm equal to 46.29 mg/kg/d in males and 57.79mg/kg/d in females based on reductions in the cumulative body weight gains at the higher dose levels.

Discussion of Tumor Data: Difenoconazole was reviewed by the HED-CPRC on May 18,1994 (memorandum of July 27, 1994 from E. Rinde of the NED CPRC to C. Giles-Parker of RD) and classified as a Category C carcinogen without a q-star. The margin-of-exposure (MOE) approach was selected because there was only very weak (limited) evidence of carcinogenic potential at dose levels not considered to be excessive with significant changes observed only at excessive doses. There was no evidence for genotoxicity. There was a statistically significant increase in liver adenomas, carcinomas, and combined liver adenomas and carcinomas in both sexes at doses of 2500 and 4500 ppm. These doses were considered to be excessively high for cancer testing. Liver necrosis and liver adenomas were also noted in males at 300 ppm. There were no statistically significant increases in liver tumors at 10 or 30 ppm. Adequacy of the Dose Levels Tested: The Health Effects Division Cancer Peer Review Committee considered the doses adequate and the study acceptable.

870.4200b Carcinogenicity (feeding) – Rat MRIDs 42090019/ -20

CGA 169374 was administered in the diet to male and female rats [80/sex/dose] for 104 weeks at 0; 10; 20; 500; and 2500 ppm. There were reductions in cumulative body weight gains in the 500 and the 2500 ppm groups. Mean liver weight was increased at week 53 and t termination in the 2500 ppm group . Hepatocellular hypertrophy was observed in the 500 and the 2500 ppm animals at termination. Additional findings in the clinical chemistry data also indicated that liver was the primary target organ for toxicity. No treatment related increased incidences of neoplastic findings were observed in this study. The NOAEL for the study was 20 ppm which was equal to 0.96 and 127 mg/kg/d for males and females respectively. The LOAEL was 500 ppm equal to 24.12 and 32.79 mg/kg/day for males and females respectively based on cumulative decreases in body weight gains. Discussion of Tumor Data No treatment related increased incidences of neoplastic findings were observed in this study. Adequacy of the Dose Levels Tested The dose levels tested were considered adequate by the Cancer Peer Review Committee. (memorandum of July 27,1994 from B. Rinde of the Health Effects Division)

A.4.6 Mutagenicity

Gene Mutation

Guideline # 870.5100 Bacterial assay 42090019, 42710010 Minimum/ guideline	Not mutagenic
Guideline #870.5300, In vitro mammalian cell gene mutation test MRID 42090024 Unacceptable Guideline	No conclusion can be reached from the three nonactivated and two S9 activated mouse lymphoma forward mutation assays conducted with difenoconazole technical. The study was seriously compromised.

Cytogenetics

Guideline # 870.5375, Clastogenicity in mammalian cells MRID 46950319, 46950321 Acceptable Guideline MRID 46950323 Guideline #870.5395 Micronucleus test in bone marrow MRID 41710011 Acceptable Guideline Guideline #870.5550 Unscheduled DNA Synthesis in Mammalian Cells in Culture 4210012 (1992) Acceptable/ guideline	There was evidence of a weak induction of structural chromosomal aberrations over background in the presence of S9-mix. There was no evidence of structural chromosomal aberrations induced over background.Mice bone marrow - No increase in micronucleated polychromatic erythrocytes occurred with CGA-169374 (91.2% a.i). CGA-169374 tech. (92.2% a.i.) was considered to be negative in the unscheduled DNA synthesis assay in rat primary hepatocytes as measured by an autoradiographic method at concentrations up to 50.0 µg/mL.

A.4.7 Neurotoxicity

870.6100 Delayed Neurotoxicity Study – Hen - NA

870.6200 Acute Neurotoxicity Screening Battery – Rat MRID 46950327

In an acute neurotoxicity study (MRID 46950327), groups of fasted Alpk:APfSD Wistar-derived rats (10/sex/dose), at least 42 days old, were given a single oral dose of difenoconazole technical (CGA169374) (94.3% w/w, batch/lot # WM806228) in 1% w/v aqueous carboxymethylcellulose (CMC) at doses of 0, 25, 200, or 2000 mg/kg bw and observed for 14 days. Dose levels selected for this study were based on the results of preliminary acute neurotoxicity study (MRID 46950325). Neurobehavioral assessment (functional observational battery and motor activity testing) was performed on 10 animals/sex/group on days -7, 1, 8, and 15. Body weight and food consumption were measured weekly throughout the study. At study termination, 5 animals/sex/group were euthanized and perfused in situ for neuropathological examination; brain weight was recorded from these animals. Of the perfused animals, 5 animals/sex from the control and high dose groups were subjected to histopathological evaluation of brain and peripheral nervous system tissues.

There were no unscheduled deaths at any dose level. Weight change on the day of dosing by the control, low-, mid-, and high-dose groups was -2.1, - 1.0, -7.8, and -18.3 g, respectively, for males and 0.0, 2.1, -3.8, and -13.0 g, respectively, for females. Body weight for females had recovered to control levels by day 8. Food consumption for males given 2000 mg/kg was approximately 20% less than control during week 1 only ($p<0.01$). Food consumption for these animals recovered to control levels during week 2. There were no differences from control for females at any dose level or for males at the lower dose levels. These effects on body weight and food consumption were not toxicologically significant.

At 2000 mg/kg, a number of adverse clinical signs were observed on day I (at the time of **peak** effect), including: upward curvature of the spine (8 males, 9 females); tip-toe gait (3, 8);

decreased activity (6, 7); piloerection (3, 5); sides pinched in (3, 7); and subdued (1, 0). Females were affected more than males. All treatment-related clinical signs observed on day 1 showed complete recovery by day 5 (males) or day 7 (females).
Significant decreases in fore-limb grip strength were seen in mid- (23%) and high-dose (26%) males on day 1. Females dosed with 2000 mg/kg had lower motor activities on day 1 (37%), at the time of peak effect, and on day 8 (31%). Males dosed with 200 or 2000 mg/kg had higher motor activities than the controls on day 1, 50% and 55%, respectively, at the time of peak effect. There were no effects on brain weight at any dose level. Neuropathological examination of the central and peripheral nervous system showed no effects of treatment at doses of 2000 mg/kg in both sexes. The LOAEL for acute neurotoxicity of difenoconazole technical (CGA169374) in male rats is 200 mg/kg bw based on reduced fore-limb grip strength in males on day 1. The NOAEL is 25 mg/kg bw. The LOAEL for acute neurotoxicity of difenoconazole technical (CGA169374) in female rats is 2000 mg/kg. Based on decreased body weight, the following clinical signs: upward curvature of the spine, tip-toe gait, decreased activity, piloerection and sides pinched in, and decreased motor activity. The NOAEL is 200 mg/kg bw.

870.6200 Subchronic Neurotoxicity Screening Battery

In a subchronic neurotoxicity study (MRID 46950329) difenoconazole technical (94.5% w/w, batch no. WM806228) was administered to groups of 12 male and 12 female Alpk:AP_fSD (Wistar-derived) rats at concentrations of 0, 40, 250, or 1500 ppm in the diet for 90 days. Respective dose levels corresponded to 0, 2.8, 17.3 or 107.0 mg/kg bw/day for males and 0, 3.2, 19.5, or 120.2 mg/kg bw/day for females. Neurobehavioral assessment (functional observational battery and motor activity testing) was performed in 12 animals/sex/group pretest and during weeks 2, 5, 9, and 14. Cholinesterase activity was not determined. At study termination, 5 animals/sex/group were euthanized and perfused *in situ* for neuropathological examination. Of the perfused animals, 5/sex from the control group and 5/sex from the 1500 ppm group were subjected to histopathological evaluation of brain and peripheral nervous system tissues. Treatment with difenoconazole at concentrations up to 1500 ppm in the diet had no effect on mortality or clinical signs. Relative to respective control weight, final body weight of males and females in the 1500 ppm group was reduced by 9% and 7%. Body weight gain was reduced by 22% in males and 23% in females. Food consumption was reduced in this group (statistically significant only in females [7%]), and food efficiency was significantly reduced in males by 21% ($p \leq 0.05$) and in females by 21% (ns). Lower dose groups were unaffected. Absolute liver weight in males and females in the 1500 ppm group was increased over respective control weight by 38% and 45%. Liver was not weighed in lower dose groups. The increase in liver weight was considered a normal response to chemical treatment.

During weeks 2, 9 and 14, hind-limb grip strength in males in the 1500 ppm group was reduced by 18 to 27% relative to the control values. At week 14, hind-limb grip strength in males in the 250 ppm group was significantly ($p \leq 0.05$) reduced by 20% relative to the control values. FOB observations in females were unaffected by treatment. Motor activity was unaffected in both sexes at all observation times. Brain weight was unaffected by treatment and there were no treatment-related neuropathological lesions.

The LOAEL in male rats is 250 ppm in the diet (17.3 mg/kg bw/day), based on decreased hind

limb strength. The NOAEL is 40 ppm (2.8 mg/kg bw/day). The LOAEL in female rats is 1500 ppm in the diet (120.2 mg/kg bw/day), based on decreased body weight, body weight gain and food efficiency. The NOAEL is 250 ppm (19.5 mg/kg bw/day). The study is classified as Acceptable/Guideline

A.4.8 Metabolism

870.7485 Metabolism – Rat

Study 1

The absorption, distribution, metabolism, and excretion of difenoconazole were studied in groups of male and, female Sprague-Dawley rats. Animals were administered a single oral gavage dose of 0.5 or 300 mg/kg [^{14}C] difenoconazole or 0.5 mg/kg unlabeled difenoconazole by gavage for 14 days followed by a single gavage dose of 0.5 mg/kg [^{14}C] difenoconazole on day 15. The test compound was labeled with [^{14}C] at either the phenyl or triazole ring.

[^{14}C] CCA 169374 was rapidly and extensively distributed, metabolized, and excreted in rats for all dosing regimens. the extent of absorption is undetermined pending determination of the extent of biliary excretion. The 4-day recoveries were 97.94-107.75% of the administered dose for all dosing groups. The elimination of radioactivity in the feces (78.06-94.61% of administered dose) and urine (8.48-21.86%) were almost comparable for all oral dose groups, with slightly higher radioactivity found in the feces of the high-dose group than the low-dose groups. This was probably due to biliary excretion, poor absorption or saturation of the metabolic pathway. The radioactivity in the blood peaked at about 24-48 hours for an dosing group. Half-lives of elimination appear to be approximately 20 hours for the low-dose groups and 33-48 hours for the high-dose group. The study results also indicate that difenoconazole and/or its metabolites do not bioaccumulate to an appreciable extent following oral exposure since all the tissues contained negligible levels (< 1%) of radioactivity 7 days postexposure.

The metabolism of difenoconazole appears to be extensive because the metabolites accounted for most of the recovered radioactivity in the excrete. Three major metabolites were identified in the feces (i.e. metabolites A, B, and C). Two of the metabolites were separated into isomers (i.e., Al, A2, B1, and B2). Metabolite C was detected only in the high-dose groups, indicating that metabolism of difenoconazole is dose-related and involves saturation of the metabolic pathway. Free triazole metabolite was detected in the urine of triazole-labeled groups and its byproduct was detected in the liver of phenyl labeled groups only. Other urinary metabolites were not characterized.

These study results indicate that distribution, metabolism, and elimination of difenoconazole were not sex related. There was a slight dose-related difference in the metabolism and elimination difenoconazole. In phenyl- and triazole-labeling studies, fecal excretion of radioactivity was higher in the high-dose animals compared to the low-dose animals, and an additional metabolite was found in the feces of the high-dose animals compared to the low-dose animals. There were no major differences in the distribution and excretion of radioactivity with labeling at the phenyl and triazole ring positions, however, there were some different metabolites

identified. The studies also showed that administration of 0.5 and 100 mg/kg difenoconazole did not induce any apparent treatment-related clinical effects.

The study is classified as acceptable guideline when considered together with data provided in additional rat metabolism studies (MRIDs 42710014, 42710013) submitted as supplemental to this study. This study may be upgraded if the following additional information is provided and is judged to be acceptable:

Study 2

These studies (MRIDs 42710014, 42710013) were submitted because EPA requested additional information not provided in the Sponsor's previously submitted metabolism studies (MRID Nos. 420900-28/29/30/31). The present studies describe the absorption, distribution, and excretion, as well as pharmacokinetics, of [^{14}C] difenoconazole after a single oral gavage dose of 0.5 or 300 mg/kg in rats (Report 1) and isolated and identified urinary metabolites in three females after a single oral gavage dose of 300 mg/kg (Report 2).

Following oral administration of 0.5 or 300 mg/kg ^{14}C-CCA 169374 in rats, the test compound was adequately absorbed and mainly eliminated via the bile; no evidence of bioaccumulation in any tissue was noted. After 48 hours, total recovery (independent of dose and sex) was ≈ 96% of the administered dose. Biliary excretion constituted the main route of elimination with some dose- and sex-dependency (≈ 75% at the low dose for both sexes; 56% for males and 39% for females at the high dose). Urinary and fecal eliminations exhibited a dose-related pattern at 48 hours. In the urine, 9-l4% was eliminated at the low dose versus 1% in the high-dose rats. In the feces, 2-4% was eliminated at the low dose versus 17-22% at the high dose. In cannulated males after 48 hours, ≈ 80% was eliminated via the bile, while ≈ 4% and ≈ 14% were eliminated via urine and feces, respectively. Therefore, this study indicates that most of the dose following oral administration is absorbed as indicated by the biliary excretion data. The dose-related difference in elimination suggests that saturation is reached at the higher dose level resulting in an increase of unabsorbed test material.

Maximum concentration in blood was reached within 2 hours at the low dose and 4 hours at the high dose. By 24 hours, <0.05 ppm equivalent was detected in the blood. Total recovery ranged from 95% to 97% after 48 hours, irrespective of dose and sex. During the first 12 hours, slight differences were evident between males and females with regard to Tmax, Cmax, and rate of elimination. The concentration in females was approximately half of that in males and was eliminated faster than in males. Mean half-lives in males and females from Tmax to 12 hours, were 6.2 and 4.4 hours, respectively; from 24 to 168 hours, they were 2.8 and 3.7 days, respectively.

Following administration of 300 mg/kg of (^{14}C-phenyl) CGA 169374, 3 major urinary metabolites were identified: sulfate conjugates (and their isomers) of HO-CGA 205375, isomers of HO-CGA 205375, and the hydroxyacetic metabolite of H0-CGA 205373. The major urinary metabolites of CGA 169374 have been identified and no single unknown metabolite accounted for >1.1% of the dose.

These studies alone do not meet the minimum requirements for Guidelines 85-1. However, these

studies combined with previously submitted studies (MRID Nos. 420900-28/29/30/31) are considered to be acceptable,

A.4.9 Immunotoxicity

870.7800 Immunotoxicity – Rat

A difenoconazole immunotoxicity has been submitted by the registrant and is under review.

A.4.1 Dermal Toxicity

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

December 18, 2008

MEMORANDUM

SUBJECT: **Difenoconazole - with both available in vivo and in vitro dermal absorption studies, select an appropriate dermal absorption factor to be used for risk assessment.**

PC Code: 128847 **DB Bar Code:** NA

FROM: Jonathan Chen, Ph.D., Senior Toxicologist Jonathan Chen 12/18/08
Jenny Tao, M.D. Senior Toxicologist 12/15/08
Risk Assessment and Science Support Branch (RASSB)
Antimicrobial Division (7510P)

TO: Marshall Swindell
Product Manager, Team #33
Regulatory Management Branch I / AD

THROUGH: Norman Cook, Branch Chief 12/18/08
RSSB/AD (7510P)

Synonym: 1-{2-{4-(4-Chlorophenoxy)-2-chlorophenyl}-4-methyl-1,3-dioxolan-2-ylmethyl}-1H-1,2,4-triazole, CGA169374

Formulation: **Difeno-Shield™**

Active Ingredient:

Difenoconazole .....32.8% a..i.

The technical ingredient has a purity of >99% a.i.

1

Applicant: Syngenta Crop Protection, Inc., Greensboro, N.C. 37419

Use: Difeno-Shield is fungistatic agent that controls and/or inhibits the growth of many fungi associated with odor, staining and discoloration. Difeno-Shield can be applied to paper, wallboard, paint, coatings, caulks, sealants, adhesives, textiles and plastic. It provides an invisible barrier to inhibit the fungal organisms associated with mold and mildew that cause odor staining and discoloration. Difeno-Shield is not intended to protect users or others against food-borne or disease causing organisms. Difeno-Shield is not for use in food or feed handling areas.

Background and Conclusion:

On October 9, 2008, there is AD Toxicity Endpoint Selection Committee special working group meeting held been held to address the appropriate way to use the *in vitro* study results. Attached is the meeting minute.

There are four Difenoconazole dermal absorption studies.
In vivo Dermal Penetration in the Rat, MRID: 47453201
In vivo Dermal Penetration in the Rat, MRID: 46950333
In vitro Absorption through Human Epidermis; MRID: 47453202
In vitro Absorption through Rat Epidermis; MRID: 47453203

The working group considers both available in vivo and in vitro dermal absorption studies, and an estimated Dermal Absorption factor of 6.0 % was decided to be used in future risk assessment.

Special Working group Meeting
AD Toxicity Endpoint Selection Committee
Potomac Yard, Room S-8621

Meeting Minutes
October 9, 2008

Attendees

Stephen Dapson ..... HED
Pv Shah ..... RD
John Redden ..... RD
Jonathan Chen ..... AD
Jenny Tao ..... AD
Michelle Centra ..... AD

This special working group of the AD Toxicity Endpoint Selection Committee (ADTC) is organized to discuss following Issues:

- The current Office of Pesticide (OPP)'s position in handling the information generated with in vitro dermal absorption studies.
- Using difenoconazole as an example, with both available in vivo and in vitro dermal absorption studies, select an appropriate dermal absorption factor to be used for risk assessment.

Jonathan Chen chaired this meeting.

Issue One: The current Office of Pesticide (OPP)'s position in handling the information generated with in vitro dermal absorption studies.

Jonathan Chen points out in creosote RED risk assessment Agency already used an approach of comparing the in vitro studies (Rat skin vs. human skin), calculated an adjustment factor, and applied to the dermal absorption factor selected from in vivo study. Both Pv Shah and Steve Dapson indicate North American Free Trade Agreement (NAFTA) did prepare a draft dermal absorption group position paper on using the in vitro dermal absorption data in risk assessment . In the draft documents, major points are listed below:

1. use of in vitro data as the sole basis for derivation of a Dermal Absorption Factor (DAF) for human health risk assessment is not recommended;
2. Under the situation when both in vitro studies (human and animal) studies and an in vivo animal study are available, the vitro data may be used to extrapolate to human equivalent DAFs for risk assessment.
3. Under this approach, if an in vitro technique performed using animal skin is shown to be a good predictor of animal in vivo dermal absorption for a particular compound, then the same technique conducted in vitro with human skin may be useful in extrapolating to humans. The relationship can be demonstrated as following formula.

IF	$\frac{\text{Animal } \textit{in vitro}}{\text{Animal } \textit{in vivo}} \approx 1$	THEN	Human *in vitro* ≈ Human DAF

Working Group Conclusion:

- Although the NAFTA's position paper is not finalized yet, PV indicated both Health Canada's Pest Management Regulatory Agency (PMRA) and HED management approved this approach. AD should consider it is an appropriate approach in using the in vitro study information;
- The approach should be evaluated on a case-by-case base; and
- In the case when the data set consisting of a "Triple Pack" of in vitro human and animal studies and an in vivo animal study conducted using identical test material can be used to extrapolate human DAF for risk assessment, using following formula

Estimated Human DAF = Adjustment Factor x Animal in vivo DAF

Where

$$\textbf{Adjustment Factor} = \frac{\textbf{Human in vitro DAF}}{\textbf{Animal in vitro DAF}}$$

Note: After the meeting, Steve Dapson sends the most recent NFTA's Draft to the group (See Attachment 1).

Issue Two: Using difenoconazole as an example, with both available in vivo and in vitro dermal absorption studies, select an appropriate dermal absorption factor to be used for risk assessment.

For difenoconazole, there are four dermal absorption studies.

In vivo Dermal Penetration in the Rat, MRID: 47453201
In vivo Dermal Penetration in the Rat, MRID: 46950333
In vitro Absorption through Human Epidermis; MRID: 47453202
In vitro Absorption through Rat Epidermis; MRID: 47453203

Four Different Steps are taken in determine the proposed DAF

Step 1. Determine the appropriate dermal absorption factor based on *in vivo* dermal absorption studies.

There are two *in vivo* dermal absorption studies. The executive summary of these two studies are listed below.

***In vivo* Study 1:**
Roberts, K. and Jones, B. (2007). Difenoconazole technical in vivo dermal penetration study in the rat. Central Toxicology Laboratory, Cheshire, UK. Report Number UR0908-REG, February 6, 2007. MRID 47453201. Unpublished.

In the dermal penetration study (MRID 47453201), Difenoconazole (99.1% a.i.) and [^{14}C] Difenoconazole (>98% a.i. radiochemical purity, Batch reference: AMS 255/4) was applied to the skin (10 cm^2) of male Han Wistar rats (16 rats/dose).

Sample doses were prepared by the Sponsor (0.5% carboxy-methylcellulose (CMC) used as vehicle) and applied at a rate of 10 $\mu L/cm^2$ as an aqueous dilution of the concentrate 1/100 (1 mg a.i./mL) or 1/10 (10 mg a.i./mL), aqueous dilutions of the concentrate or as a concentrate (100 mg a.i./mL), corresponding to applied nominal doses of 10, 100, or 1000 $\mu g/cm^2$, respectively.

Exposure duration was 10 hours after application and animals were monitored up to 72 hours post-dosing. Subgroups of rats (4/dose) were terminated at 10, 24, 48, and 72 hours post-dosing. Skin washings, application site materials, excreta, selected tissues, blood and animal carcasses were analyzed for radioactivity.

The majority of the applied doses (80-92%) remained on the skin surface and was readily removed with mild washing indicating that aqueous solutions of [^{14}C]-difenoconazole are poorly absorbed through rat skin. Absorption of [^{14}C]-difenoconazole, though minimal, generally, increased over time for all applied dose concentrations.

Mean Combined Absorption values of [^{14}C]-difenoconazole from the 0.1% (1 mg/ml/10 ug/cm^2) dose was 11.3%, 13.8%, and 13.0% at 10, 24, and 72 hours, respectively. Mean Combined Absorption values of [^{14}C]-difenoconazole from the 1% (10 mg/ml/100 ug/cm^2) dose was 4.1%, 4.3%, and 5.3% at 10, 24, and 72 hours, respectively. Mean Combined Absorption values of [^{14}C]-difenoconazole from the 10% (100 mg/ml, concentrate/1000 ug/cm^2) dose was 1.4%, 2.4%, and 2.8% at 10, 24, and 72 hours, respectively.

For this study, the working group decides a dermal absorption factor of 13.8% (0.1% , 24 hours after exposure) should be the appropriate dermal absorption factor.

***In vivo* Study 2:**
Hassler, S. (2003). Difenoconazole 250 EC (A7402G): Dermal absorption of [Triazole-U-14C] CGA 169374 formulated as Score® 250 EC (A-7402G) in the rat (in vivo). Syngenta Crop Protection AG, CH-4002 Basel, Switzerland. Report Number 051AM-1, May 6, 2003. MRID 46950333. Unpublished.

In the *in vivo* dermal penetration study (MRID 46950333), [Triazole-U-^{14}C] CGA 169374 formulated as SCORE® 250 EC (Batch No. ILA 50.2-1, ILA 50.2-2 (radiolabeled, >98%a.i.)

and AMS 255/3 (non-radiolabeled, >98%a.i.) was applied to the skin (10 µL/cm^2) of 4 male HanBrl: WIST (SPF) rats/dose/treatment at three dose levels: 0.5 (P1), 13 (P2), 2.5µg/cm^2 (P3 and P3a). The results of the high dose level (Group P3) showed a high variability in the efficiency of the washing procedure which did not allow for reliable evaluation of dermal absorption; therefore the high-dose dermal application was repeated and assigned as Group P3a. The nominal exposure duration was 6 hours, at which time the dermal absorption of the test substance was determined. The amount remaining in/on the skin at the application site after washing was determined at three additional time points 24, 48, or 72 hours after application in order to estimate the depletion of the dose. Urine, feces, and blood were collected. The applied concentrations of the low and medium dosages were intended to approximate realistic concentrations recommended for use in the field, whereas the high dose was undiluted product.

Recoveries of the applied doses were 95-104%. The **Total Mean Combined Absorbed Dose** (%) over a specific time period was calculated as exposed skin site (skin strips and remaining treated skin) plus excreta (urine, feces, and cage wash), carcass (all organs), and blood had conflicting results across the doses. After the 6 hour exposure 27, 13, and 9% of the dose was totally absorbed (skin, whole blood, g.i. tract, remaining carcass, feces urine) in the low, mid-, and high-dose group, respectively. At 24 hours, after exposure 6 hour of low, mid- and high dose groups would be 48, 19 and 8 % of the total absorbed dose.

However there was a high level of variation between individual animals in the same dose group. The low and mid-dosed animals show an increase in absorbed dose from 6 to 24 hours and a slight decrease at 48 and 72 hours. However, the high-dose group did not show an increase from 6 until 48 hours with a substantial decrease in radioactivity at 72 hours. The majority of the absorbed radioactivity was isolated in the gastrointestinal tract or carcass at 6 and 24 hour, with increasing amounts found in the feces at 48 and 72 hours. Blood residues during and after dermal exposure at all doses were mostly at or below the limit of detection, the highest blood residues levels were reached between 6 and 8 hours after administration, accounting for 0.01 ppm and 0.25 ppm CGA 168374 equivalents for the middle and high dose levels, respectively. The majority of the radioactivity was washed off and the rinsate was analyzed as CGA 169374 equivalents.

For this study, the working group decides a dermal absorption factor of 48 % (0.5 µg/cm^2 , 24 hours after exposure) should be the appropriate dermal absorption factor.

In conclusion, the working group decides a dermal absorption factor of 48 % should be the appropriate dermal absorption factor based on the *in vivo* dermal absorption studies (MRIDs 47453201 and 46950333).

Step 2. Determine the appropriateness of the in *in vitro* dermal absorption studies.

There are two *in vitro* dermal absorption studies: *in vitro* Absorption through human epidermis (MRID: 47453202) and *in vitro* absorption through rat epidermis (MRID: 47453203). Working group concluded that in the calculation of the dermal absorption, the percent dermal absorption should include the chemical concentration absorbed in the epidermis and amount in receptor fluid. The two studies are summarized below.

***In vitro* Study 1:**

Gledhill, A. (2007). Difenoconazole technical: In vitro absorption through rat epidermis final report. Report Number JV1923-REG0R2, June 28, 2007. MRID 47453203. Unpublished.

In a dermal penetration study (MRID 47453203) Difenoconazole (99.1% a.i.) and [^{14}C] Difenoconazole (>98% a.i. radiochemical purity, Batch reference: AMS 255/4) was applied to the epidermal membranes of male rats of the Wistar Crl: (WI)BR strain at a rate of 10 µL/cm2 as preparations representing an 10, 100, or 1000 µg/cm2. Exposure duration was 10 or 24 hour periods, during which receptor fluid was sampled at specific time intervals. Any difenoconazole remaining on the skin after the two exposure periods was removed by washing.

For the 10-hour exposure period, the percent dermal absorbed are 26%, 2.8% and 2.9 % of the applied dose of 10, 100, or 1000 µg/cm2, respectively. For the 24-hour exposure period, the percent dermal absorbed are 40%, 17% and 3.3 % of the applied dose of 10, 100, or 1000 µg/cm2, respectively. The Study Results for the 24-hours post application is summarized in Table 1.

Table 1 Summarize the Difenoconazole in each matrix at 24 hours post-application from in vitro Rat dermal absorption study (Gledhill, 2007, MRID 47453203)

Matrix analyzed	Amount of difenoconazole in each matrix 24 hours post-application		
	Percent of Applied Does (mean ± SEM)		
	1000 µg/cm^2 (n=5)	100 µg/cm^2 (n=6)	10 µg/cm^2 (n=5)
Donor chamber	0.21 ± 0.19	0.40 ± 0.30	0.29 ± 0.14
Skin wash	98.7 ± 1.58	73.9 ± 3.97	52.8 ± 3.35
Epidermis	2.37 ± 0.67	14.8 ± 2.01	2.51 ± 0.51
Amount in receptor fluid	0.91 ± 0.25	3.67 ± 0.63	37.1 ± 2.55
Total Recovery	102 ± 1.52	93.1 ± 5.82	92.7 ± 1.13
Percent dermal Absorption [1]	3.3%	17%	40%

Note: 1. Percent Dermal Absorption = the total Amount of difenoconazole in epidermis and amount in receptor fluid.

In vitro Study 2:

Davies, D. (2007). *In Vitro* absorption through human epidermis final report. Central Toxicology Laboratory, Cheshire,UK. Report Number JV1922-REG-R1, January 26, 2007. MRID 47453202. Unpublished.

In a dermal absorption study (MRID 47453202), Difenoconazole (99.1% a.i.) and [14C] Difenoconazole (>98% a.i. radiochemical purity, Batch reference: AMS 255/4), was administered to human epidermal membranes at a rate of 10 µL/cm2 as preparations representing a 10, 100, or 1000 µg/cm2. Exposure duration was 10 or 24 hour periods, during which receptor fluid was sampled at specific time intervals. Any difenoconazole remaining on the skin after the two exposure periods was removed by washing.

The applications in this study were designed to simulate potential human dermal exposure arising from the normal use of this type of formulation. The distribution of difenoconazole absorption in the skin was determined for 10 and 24 hours, and a 24 hour absorption profile (µg/cm2/h) was determined. At 10 hours, absorption was 3.46%, 1.15%, and 0.44% for 10, 100, and 1000 µg/cm2, respectively. At 24 hours, the absorption was 4.54%, 1.30%, and 0.40% for the 10, 100, and 1000 µg/cm2, respectively. The Study Results for the 24-hours post application is summarized in Table 2.

Table 2. Summary of the Difenoconazole in Each Matrix at 24 hours Post-application from *in vitro* Human Dermal Absorption study (Davis, 2007).

Matrix analyzed	Amount of difenoconazole in each matrix 24 hours post-application		
	Residues in matrix (Mean % of applied dose) [1]		
	1000 µg/cm^2	100 µg/cm^2	10 µg/cm^2
Donor chamber	0.02	0.14	0 .17
Skin wash	96.4	81.6	102
Stratum corneum	0.16	0.52	0.50
Remaining epidermis	0.15	0.35	0.70
Amount in receptor fluid	0.09	0.43	3.34
Total Recovery (sum of above)	96.8	83.0	107
Percent dermal Absorption [2]	0.40 %	1.30%	4.54%

Note: 1. Mean of 6 samples/group.
2. Percent Dermal Absorption = The total Amount of difenoconazole in Stratum corneum, remaining epidermis and Amount in receptor fluid.

In the discussion, following limitations in the both of the two *in vitro* studies are identified.

1. After the skin sample is carefully removed from the site, the skin was soaked in 1.5 M sodium bromide for 20 minutes and rinsed after soaking with distilled water, and the epidermis was peeled from the dermis. Working group suggested that it would have better to dermatomed the skin (350-450 micron) rather than chemical separating , should be included in the dermal absorption study; and

2. The epidermis is stored frozen in aluminum foil until it is needed. Although the membrane integrity was determined by measurement of the electrical resistance across the skin membrane: membranes with a measured resistance, working group still consider freezing of the skin sample is not recommended.

However, because limitations of the dermal absorption studies are similar between the *in vitro* rat dermal absorption and the *in vitro* human dermal absorption study, and the *in vitro* rat DAF is equivalent to the rat in vivo DAF. Therefore, working group concluded that the in vitro dermal absorption studies are appropriate to be used to establish DAFs for risk assessment.

Step 3. Identify the appropriate Adjustment Factor for extrapolating from Rat DAF to Human DAF,

Working group decides the 24-hour exposure period is more appropriate in comparing the difference between in vitro rat *vs.* human skin studies. Table 1 summarizes the difenoconazole in each matrix at 24 hours post-application from in vitro rat dermal absorption study (Gledhill, 2007, MRID 47453203). Table 3 summarizes the calculated ratio of in vitro human dermal absorption factor vs. in vitro rat dermal absorption of difenoconazole .

Table 3. Summarize the Calculated Ratio of *in vitro* Human Dermal Absorption Factor (DAF) vs. *in vitro* Rat Dermal Absorption Factor of Difenoconazole .

Calculated DAF	Percent dermal Absorption		
	1000 µg/cm^2	100 µg/cm^2	10 µg/cm^2
In vitro Human DAF [1]	0.40 %	1.30 %	4.54 %
In vitro Animal DAF [2]	3.3 %	17 %	40 %
Ratio	0.12	0.07	0.11

Note: 1. Derived from the summary of the Rat dermal absorption study (Gledhill, 2007, MRID 47453203), Table 1.
2. Derived from the summary of Human Dermal Absorption study ((Davis, 2007, MRID 47453202), Table 2.

Step 4. Calculation of the Estimated Dermal Absorption Factor

The Working group decides data set give the highest ratio should be used as the adjustment factor. Therefore, the dataset derived from 1000 $\mu g/cm^2$ which gave the highest ratio of 0.12 should be used for the derivation of the estimated human dermal absorption factor.

Therefore, based on the formula

Estimated Human DAF = Adjustment Factor x Animal in vivo DAF

$$= 0.12 \times 48\% = 5.76\% \text{ (Ca. 6\%)}$$

Therefore, a human estimated DAF of ca. 6 % should be used for risk assessment.

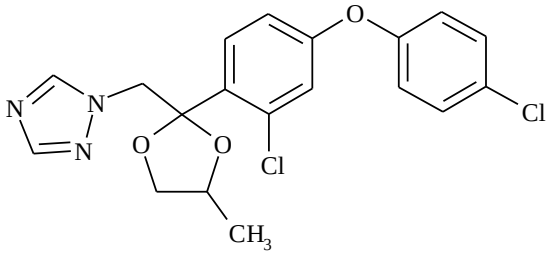
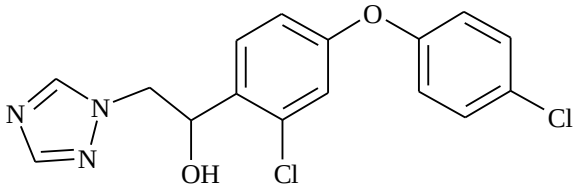
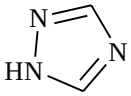
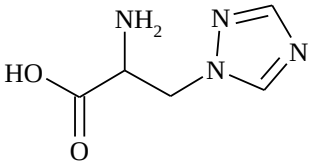
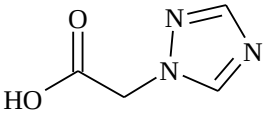
Working Group Conclusion:

Considering both available *in vivo* and *in vitro* dermal absorption studies, an estimated Dermal Absorption factor of 6.0 % should be used in future risk assessment.

B. METABOLISM

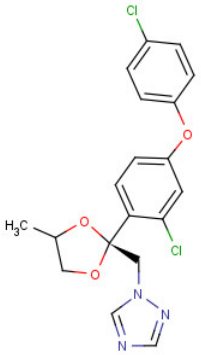
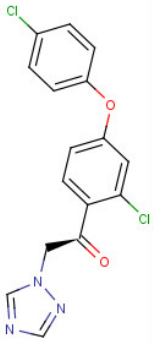
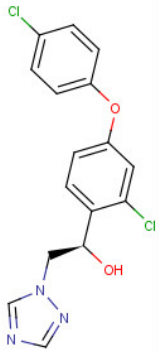
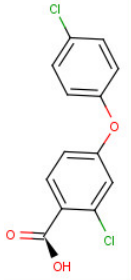
B.1 Chemical Names And Structures

Table B.1 Difenoconazole Nomenclature.

Chemical structure	
Common name	Difenoconazole
Company experimental name	CGA-169374
IUPAC name	1-({2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-yl}methyl)-1H-1,2,4-triazole
CAS name	1-[[2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole
CAS registry number	119446-68-3
Chemical structure of CGA-205375 livestock metabolite	
Chemical structure of 1,2,4-Triazole (1,2,4-T)	
Chemical structure of Triazolylalanine (TA)	
Chemical structure of Triazolylacetic acid (TAA)	

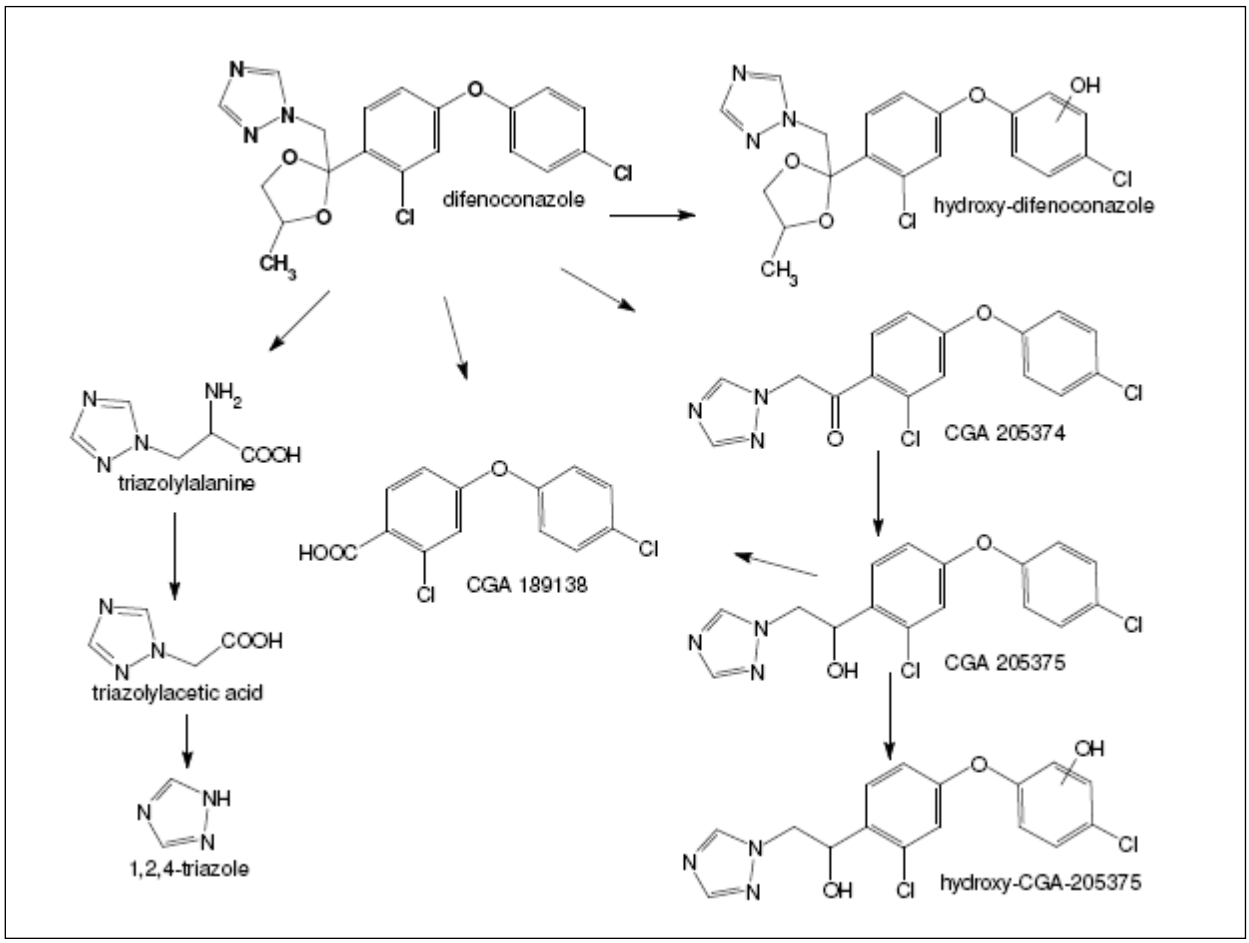
B.2 Metabolism Summary Table

Table B.2 Maximum Residues of CGA-205374, CGA-205375, and CGA-189138 in Metabolism Studies Reflecting Foliar Appls. Note: Excludes data reflecting 0-day PHIs (parent was >85% of TRR) and RACs having no detectable residues of the subject metabolites.

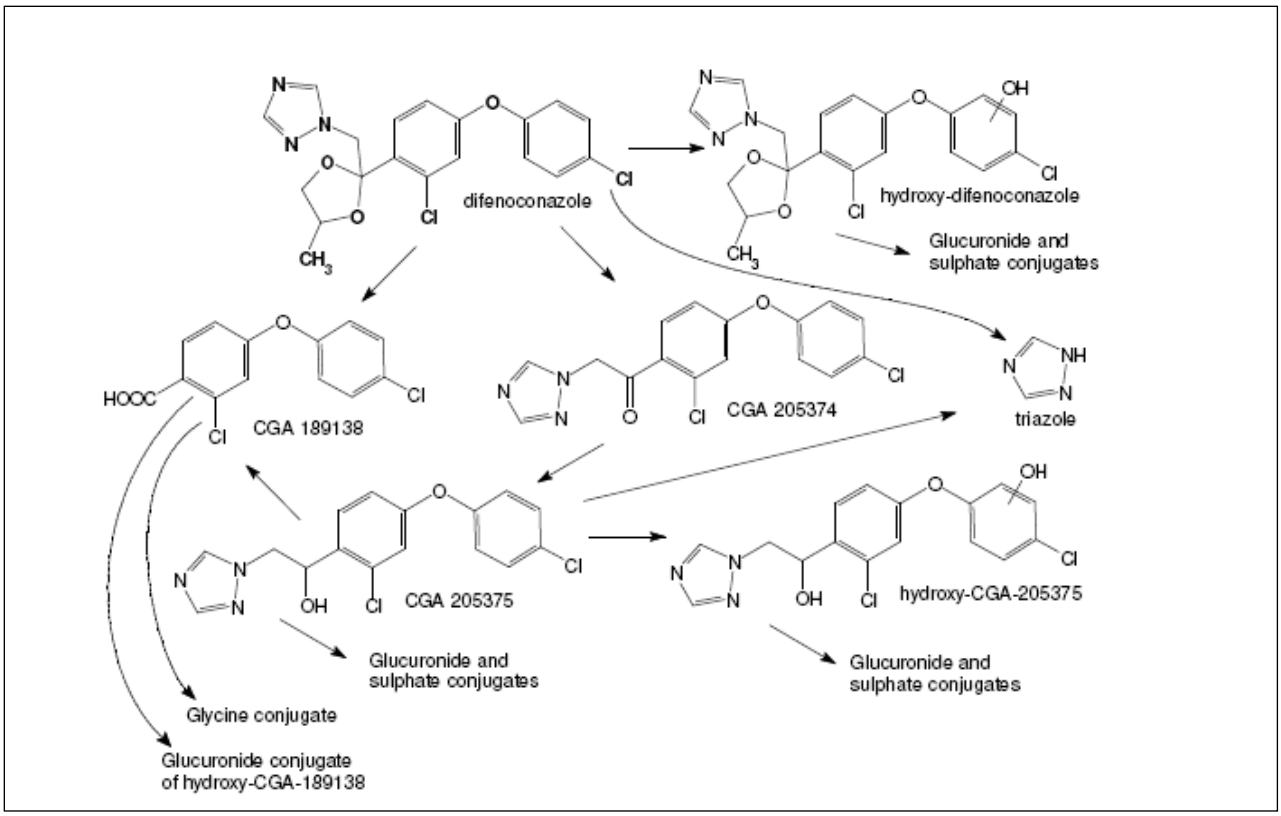
Crop [MRID Citation]	RAC	Radiolabel Position	Number of Appls. Times Rate (lb ai/A)	PHI (days)	Residues Expressed as ppm (% of TRR)			
					Difenoconazole 	CGA-205374 	CGA-205375 	CGA-189138 
Wheat [42090032]	Stalks	^{14}C Phenyl	4 x 0.22	29	23 (50%)	--	--	--
		^{14}C Triazole			27 (50%)	--	2.7 (5%)	--
Canola (Rape seed) [44701701] [44701702]	Stalks	^{14}C Phenyl	2 x 0.11	53	0.745 (17.3%)	--	0.608 (14.1%)[1]	0.069 (1.6%)[2]
		^{14}C Triazole			0.828 (17.1%)	0.058 (1.2%)[2]	0.828 (17.1%)[1]	--
	Pods	^{14}C Phenyl			0.570 (18.1%)[1]	0.009 (0.3%)[2]	0.340 (10.8%)[1]	0.054 (1.7%)[2]
		^{14}C Triazole			0.814 (17.3%)[1]	0.038 (0.8%)[2]	0.612 (13.0%)[1]	--
	Seed	^{14}C Phenyl			0.022 (14.4%)	--	0.012 (7.9%)	0.0004 (0.3%)
		^{14}C Triazole			0.093 (4.1%)	--	0.014 (0.6%)	--
Potato[3] [42090036]	Foliage	^{14}C Phenyl	6 x 0.11	12	9.47 (76.4%)	0.14 (1.1%)	0.27 (2.2%)	0.07 (0.5%)
	Tuber	^{14}C Phenyl			0.001 (8.7%)	0.0004 (3.1%)	0.0004 (3.0%)	--
Tomato [42090035]	Foliage	^{14}C Phenyl	3 x 0.22	40	1.1 (31%)	0.12 (3.4%)		0.18 (5.2%)
		^{14}C Triazole			2.1 (28%)	0.32 (4.3%)		--
		^{14}C Phenyl	2 x 0.22	14	1.3 (59.1%)	0.08 (3.8%)		0.09 (4.3%)
		^{14}C Triazole			1.5 (52.1%)	0.10 (3.5%)		--
Tomato [42090038] [42090039]	Foliage	^{14}C Phenyl	6 x 0.11	35	5.36 (64.7%)	0.32 (3.9%)	0.20 (2.4%)[4]	0.08 (0.9%)
		^{14}C Triazole			5.25 (68.0%)	0.13 (1.63%)	0.76 (9.8%)[5]	--
	Fruit	^{14}C Phenyl			0.11 (66.3%)	0.002 (1.4%)	0.005 (2.6%)[6]	--
		^{14}C Triazole			0.10 (50.9%)	0.001 (0.52%)	0.002 (0.74%)	--
Grape [43673201]	Fruit	^{14}C Phenyl	3 x 0.22	20	0.065 (51.2%)	0.005 (4.1%)	0.008 (6.6%)	0.005 (4.0%)
		^{14}C Triazole	5 x 0.22		0.052 (45.1%)	0.002 (1.7%)	0.004 (3.5%)	--
	Leaves	^{14}C Phenyl	3 x 0.22		4.260 (46.4%)	0.762 (8.3%)	0.395 (4.3%)	0.487 (5.3%)
		^{14}C Triazole	5 x 0.22		1.821 (31.5%)	0.173 (3.0%)	0.225 (3.9%)	--

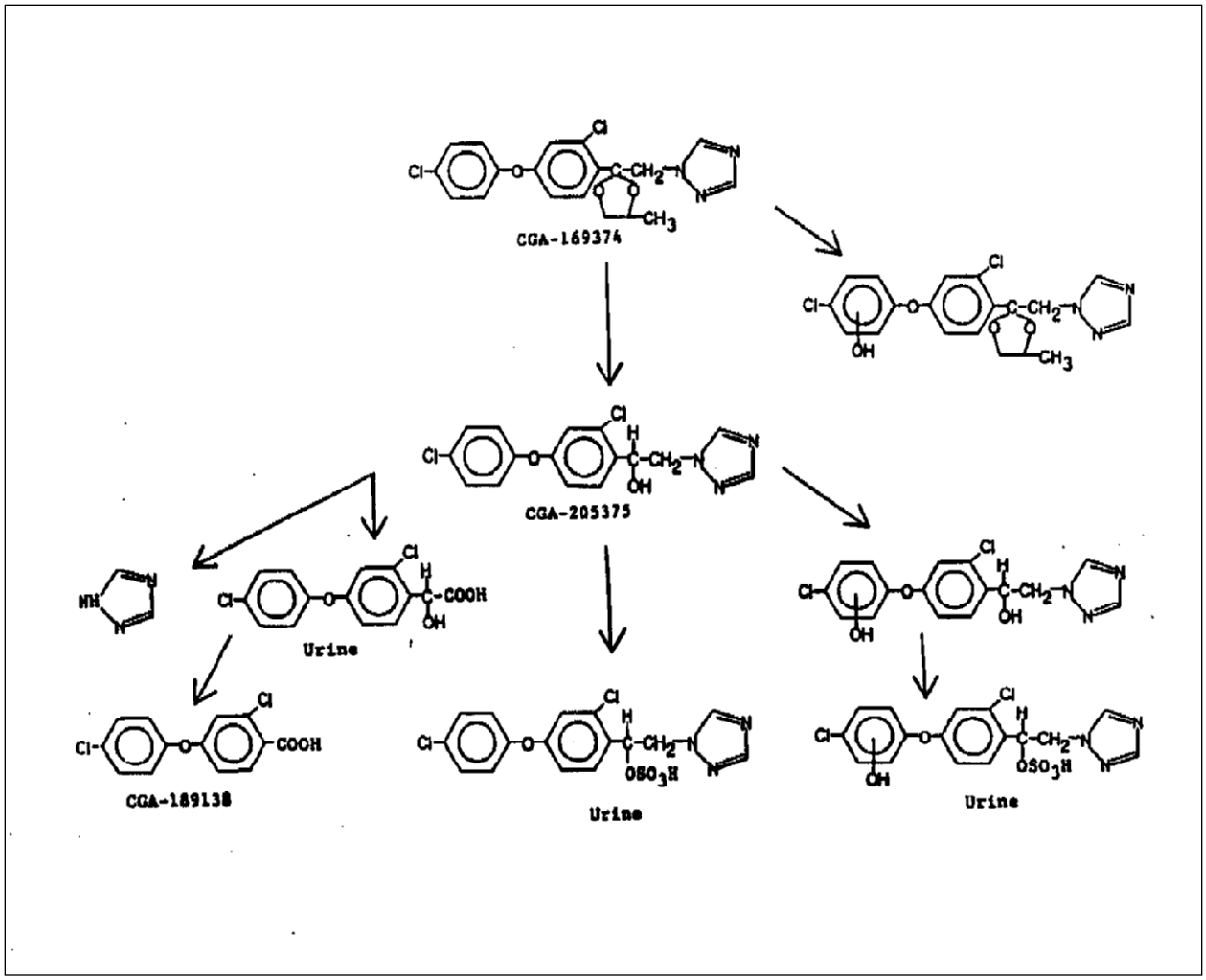
B.3 Metabolic Pathways

Plant

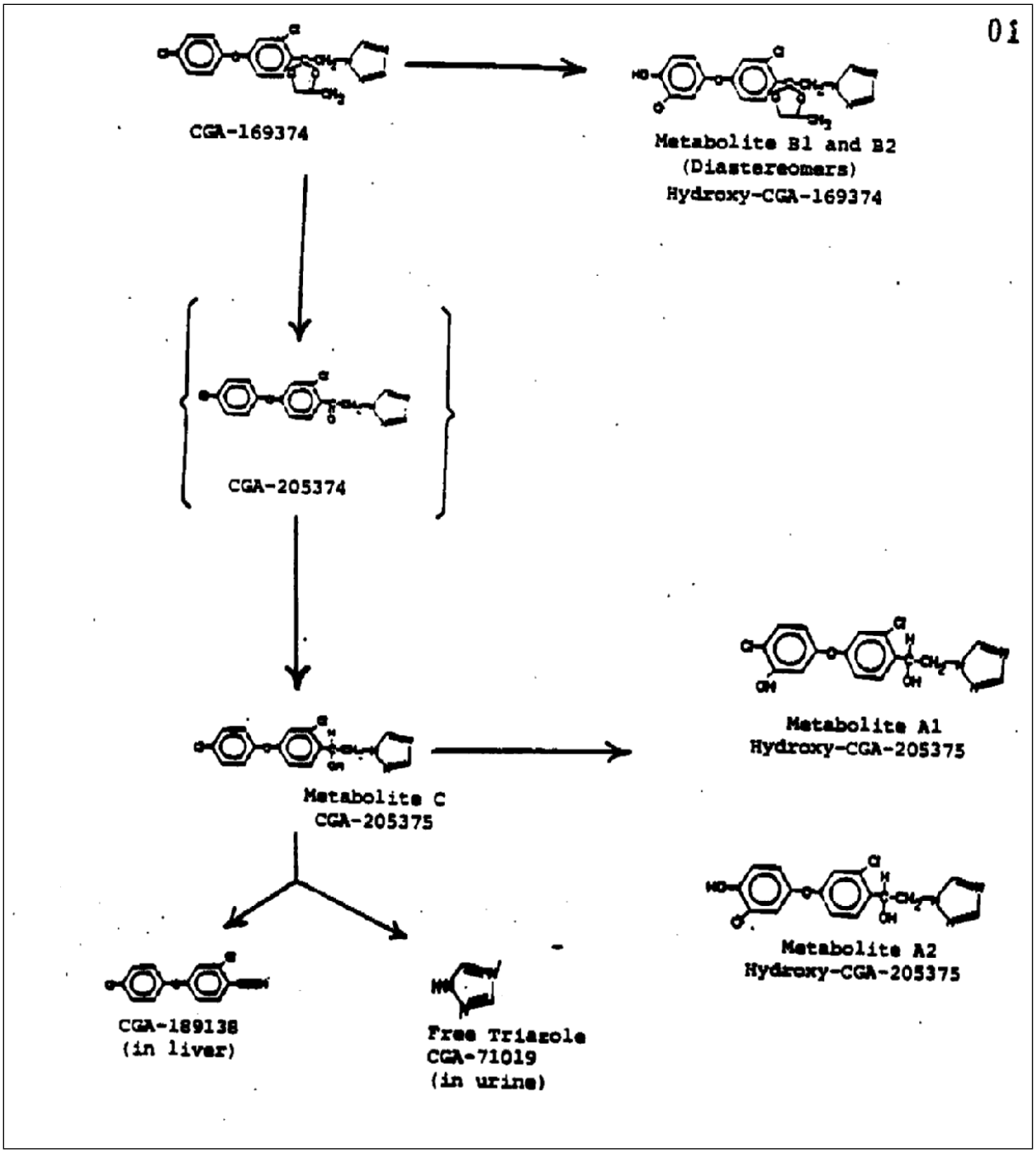


Goat Metabolism

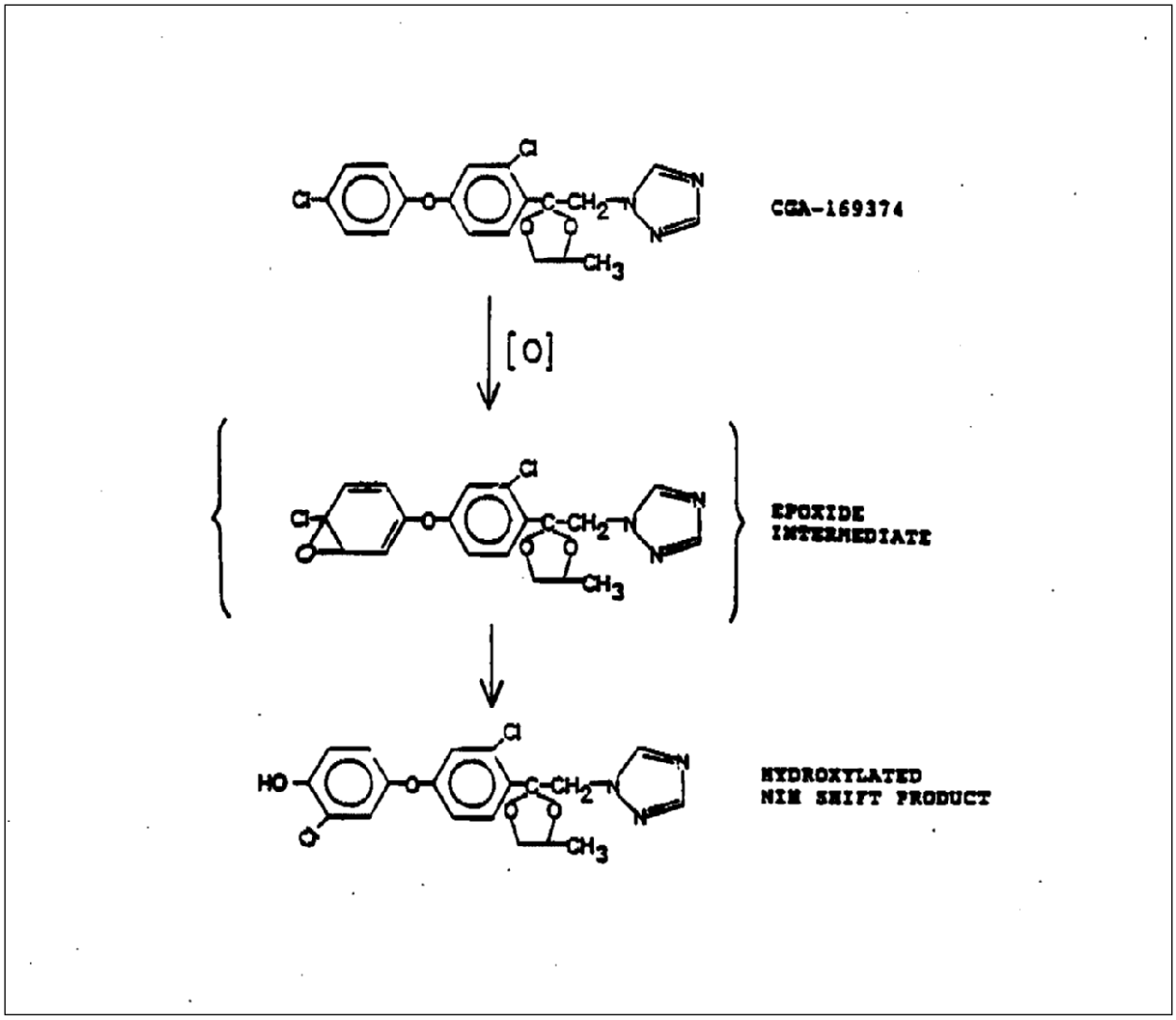




Proposed metabolic pathway in the rat (urine)



Proposed metabolic pathway in rat (feces). The ketone, CGA-205374, is presented as an intermediate from parent to CGA-205375.



Proposed mechanism for formation of metabolites A & B by the NIH Shift

C. PHYSICAL/CHEMICAL PROPERTIES

Table C.1 Physicochemical Properties of Difenoconazole.		
Parameter	**Value**	**Reference**
Melting point	78.6 ºC	DP#s 172067 and 178394, 10/26/92, R. Lascola
pH	6-8 at 20 ºC (saturated solution)	
Density	1.37 g/cm^3 at 20 ºC	
Water solubility	3.3 ppm at 20 ºC	
Solvent solubility	g/100 mL at 25 ºC: n-hexane: 0.5 1-octanol: 35 toluene: 77 acetone: 88 ethanol: 89	
Vapor pressure	2.5 x 10^{-10} mm Hg at 25 ºC	
Dissociation constant, pK_a	pure grade (99.3% ± 0.3%) difenoconazole in water (with 4% methanol) at 20ºC is 1.1	DP# 375159, 5/26/10, B. Cropp-Kohlligian
Octanol/water partition coefficient, Log(K_{OW})	4.2 at 25 ºC	DP#s 172067 and 178394, 10/26/92, R. Lascola
UV/visible absorption spectrum	λ_{max} at about 200 and 238 nm (in methanol at 26 ºC)	PMRA Proposed Regulatory Decision Document on Difenoconazole, 4/14/99 (PRDD99-01)

D. REVIEW OF HUMAN RESEARCH

Klonne, D. (1999) Integrated Report for Evaluation of Potential Exposures to Homeowners and Professional Lawn Care Operators Mixing, Loading, and Applying Granular and Liquid Pesticides to Residential Lawns: Lab Project Number: OMA005: OMA001: OMA002. Unpublished study prepared by Riceerca, Inc., and Morse Laboratories. 2213 p. (MRID 44972201).

The PHED Task Force, 1995. The Pesticide Handlers Exposure Database, Version 1.1. Task Force members Health Canada, U.S. Environmental Protection Agency, and the National Agricultural Chemicals Association, released February, 1995.